SJVDP LIBRARY 5614

See MP Library No. 14016

AGRICULTURAL DRAINAGE WATER CONTAMINATION in the SAN JOAQUIN VALLEY

A PUBLIC HEALTH PERSPECTIVE

prepared
under contract for the

Federal-State
San Joaquin Valley
Drainage Program

August 1988

This report presents the results of a study conducted for the Federal-State Interagency San Joaquin Valley Drainage Program. The purpose of the report is to provide the Drainage Program agencies with information for consideration in developing alternatives for agricultural drainage water management. Publication of any findings or recommendations in this report should not be construed as representing the concurrence of the Program agencies. Also, mention of trade names or commercial products does not constitute agency endorsement or recommendation.

The San Joaquin Valley Drainage Program was established in mid-1984 as a cooperative effort of the U.S. Bureau of Reclamation, U.S. Fish and Wildlife Service, U.S. Geological Survey, California Department of Fish and Game, and California Department of Water Resources. The purposes of the Program are to investigate the problems associated with the drainage of irrigated agricultural lands in the San Joaquin Valley and to formulate, evaluate, and recommend alternatives for the immediate and long-term management of those problems. Consistent with these purposes, Program objectives address the following key areas: (1) Public health, (2) surface- and groundwater resources, (3) agricultural productivity, and (4) fish and wildlife resources.

Inquiries concerning the San Joaquin Valley Drainage Program may be directed to:

San Joaquin Valley Drainage Program
2800 Cottage Way, Room W-2143
Sacramento, California 95825-1898

AGRICULTURAL DRAINAGE WATER CONTAMINATION in the SAN JOAQUIN VALLEY: A PUBLIC HEALTH PERSPECTIVE FOR SELENIUM, BORON, AND MOLYBDENUM

Prepared for the

San Joaquin Valley Drainage Program
2800 Cottage Way, Room W-2143
Sacramento, CA 95825-1898

Under
U.S. Bureau of Reclamation
Cooperative Agreement No. 7-FC-20-04830

By
Susan A. Klasing, Ph.D.
Susan M. Pilch, Ph.D.

Health Officers Association of California
926 J Street, Suite 201
Sacramento, CA 95814

August 1988

SUMMARY

This report reviews the public health implications of agricultural drainage water contamination in the western San Joaquin Valley for the elements selenium, boron, and molybdenum. These elements were chosen for review because they have been selected as priority substances-of-concern in agricultural drainage water by several state and federal agencies. Substances-of-concern are distinguished from other naturally occurring elements because their local concentrations may be sufficient to threaten animal or plant life. Several small studies have been conducted in the past that were useful for determining potential impacts of drainage water on public health in the area. These studies were reviewed; data and findings were appropriately incorporated into the public health reviews for each element. Additionally, much data have been collected in conjunction with the San Joaquin Valley Drainage Program for the purposes of Program planning, analysis, and decision-making; some of these data are very useful for analyzing potential human exposures to drainage contaminants and are included in the public health review chapters. In depth toxicological profiles for each of the three elements are provided in Appendices A, B, and C. This information has been combined with available exposure information to predict, where possible, the likelihood of excessive human exposure to each of the elements.

For selenium, evidence gathered to date indicates that some fish and wildlife in limited regions of the western San Joaquin Valley have accumulated sufficient tissue selenium concentrations that unlimited ingestion of such animals may be harmful to some individuals. Health advisories have been issued by state and local authorities recommending consumption restrictions for fish and wildlife in affected areas. Although limited in scope, evaluation of selenium in local produce and livestock has shown selenium concentrations to be within acceptable ranges. Similarly, most domestic water supplies surveyed in the western San Joaquin Valley do not exceed established limits for selenium in drinking water. Providing geologic and hydrologic conditions remain stabilized (or are mitigated with respect to drainage contaminants) and health advisories are adhered to by the public, current information indicates that it is unlikely that selenium overexposure (from environmental sources) is a public health problem in the western San Joaquin Valley.

For boron, information regarding both predicted health correlates from various boron exposures and the levels of human boron exposure in the western San Joaquin Valley is inadequate for decision-making purposes. Ground and surface waters in the western San Joaquin Valley are known to contain levels of boron that are far higher than national norms, but concentrations in domestic food sources are not available. Some human and animal studies have indicated adverse male reproductive effects from very high levels of dietary boron; however, the acute and/or chronic dose shown to elicit such effects is conflicting. In order to assess the potential consequence of human exposure to environmental boron compounds, additional studies are necessary to delineate more closely dose-response effects as well as the level of boron ingestion in persons residing in the western San Joaquin Valley.

For molybdenum, estimates of human dietary exposure in the San Joaquin Valley are extremely limited. Some domestic wells in the western Tulare Basin region contain molybdenum concentrations as high as 160 ppb. Because of the interference of some compounds with molybdenum analysis, concern has been

expressed that San Joaquin Valley molybdenum data may be underestimated in some cases. State or federal drinking water standards have not been set for molybdenum, but 160 ppb molybdenum in drinking water would provide 64% of the maximum "safe and adequate" intake (500 ug/day) for this element from water alone. Molybdenum concentrations in domestic food in the western San Joaquin Valley are not available. Few studies have been published that investigate the significance of molybdenum ingestion above dietary requirements. One study has reported that copper excretion may increase approximately 3-fold in subjects consuming 540 ug molybdenum/day in the form of high-molybdenum sorghum. Thus, results indicate that excessive dietary molybdenum could induce low or marginal copper status in some individuals. Additional data regarding public exposure to molybdenum and possible health correlates from exposure above the physiological requirement for this nutrient are necessary before a complete public health evaluation can be made.

Acknowledgments

The authors gratefully thank members of the Public Health Subcommittee of the Interagency Technical Advisory Committee: Dr. Raymond Neutra, Dr. Anna Fan, Dr. Lynn Goldman, and Dr. Richard Jackson, California Department of Health Services (CDHS); Riley Peters, Jeff Palsgaard, and Dr. Richard Welch, Merced County Health Department; Dr. Karl Longley, California State University-Fresno; Dr. Bruce Eldridge, University of California-Davis; Dr. Richard Jacobs, U.S. Food and Drug Administration; Kay Stahl and Dr. Donn Cobb, Fresno County Health Department; Dr. Sheldon Freedman, Kern County Medical Center; Dr. Phyllis Mowry, Fresno Community Hospital Medical Center; Dr. Michael MacLean; Tulare County Department of Health Services; Dr. Jane Valentine, University of California-Los Angeles; and Dr. Leon Hebertson, Kern County Health Department. We are especially grateful to Dr. Edwin Lee for his service as the Contracting's Officers Technical Representative and for his liaison with the San Joaquin Valley Drainage Program (SJVDP). Additionally, we are thankful to Dr. Michael DiBartolomies, Toxicology Research International, for serving as a liaison between the Citizen's Advisory Committee and the Public Health Subcommittee and to Dr. Robert Horton, SJVDP, for his support.

We appreciate the compilation of local mineral exposure tables in Chapters 4, 5, and 6 by Joy Wisniewski, HOAC.

We are especially thankful for the tireless contribution of data and insight from Walter Swain, U.S. Geological Survey, and Stephen Moore, U.S. Fish and Wildlife Service, both with the SJVDP.

We also owe a special debt to Dr. Gerald Combs, Jr., Cornell University, for his expert review of the selenium appendix.

TABLE OF CONTENTS

Page

Summary i

Acknowledgements iii

1. The Agricultural Drainage Water Problem: Scope and Limitations of Public Health Analyses 1

2. Previous Public Health-Related Studies in the San Joaquin Valley 5

3. Sources of Data for Current Health Assessments 9

4. Public Health Review of Data and Data Gaps for Selenium in the Western San Joaquin Valley 17

5. Public Health Review of Data and Data Gaps for Boron in the Western San Joaquin Valley 31

6. Public Health Review of Data and Data Gaps for Molybdenum in the Western San Joaquin Valley 37

Appendix A - Selenium
- I. Introduction A-1
- II. Occurrence A-1
- III. Environmental Fate A-2
- IV. Essentiality/Biological Function A-5
- V. Toxicokinetics A-6
- VI. Toxicity A-9
- VII. Treatment A-18
- VIII. Typical Exposure Limits/Body Burden/ Toxic Limits A-18
- IX. Indicators of Excessive Accumulation A-19
- X. Special Considerations A-22
- References A-23

Appendix B - Boron
- I. Introduction B-1
- II. Occurrence B-1
- III. Environmental Fate B-2
- IV. Essentiality/Biological Function B-5
- V. Toxicokinetics B-5
- VI. Toxicity B-7
- VII. Treatment B-14

VIII. Typical Exposure Limits/Body Burden/ Toxic Limits B-14
IX. Indicators of Excessive Accumulation B-15
X. Special Considerations B-16
References B-19

Appendix C - Molybdenum

I. Introduction C-1
II. Occurrence C-1
III. Environmental Fate C-2
IV. Essentiality/Biological Function C-6
V. Toxicokinetics C-8
VI. Toxicity C-11
VII. Treatment C-18
VIII. Typical Exposure Limits/Body Burden/ Toxic Limits C-18
IX. Indicators of Excessive Accumulation C-19
References C-23

LIST OF TABLES

Page

Table 1. Examples of Selenium Concentrations in and Human Exposures from Consumption of Livestock, Fish, and Wildlife in the Western San Joaquin Valley . . . 19

Table 2. Examples of Selenium Concentrations in and Human Exposure from Consumption of Agricultural Crops in the Western San Joaquin Valley 22

Table 3. Portion Size Averages for Exposure Estimates 23

Table 4. Potential Relative Contribution of Different Routes of Increased Se Exposure in the Western San Joaquin Valley 25

Table 5. Human Health Effects Associated with Se Exposures 28

Table 6. Examples of Boron Concentrations in and Human Exposures from Consumption of Fish in the Western San Joaquin Valley 32

Table 7. Potential Relative Contribution of Different Routes of Increased Boron Exposure in the Western San Joaquin Valley 34

Table 8. Human Health Effects Associated with Boron Exposures 36

Table 9. Examples of Molybdenum Concentrations in and Human Exposures from Consumption of Fish in the Western San Joaquin Valley 38

Table 10. Potential Relative Contribution of Different Routes of Increased Mo Exposure in the Western San Joaquin Valley 39

Table 11. Human Health Effects Associated with Molybdenum Exposures 41

Table C.1. Transfer of Molybdenum in the Environment C-5

Table C.2 Normal Molybdenum Concentrations in Animal Tissues in ppm on a Dry-Weight Basis C-10

Table C.3. Acute Molybdenum Toxicity C-13

Table C.4. Blood Molybdenum, Xanthine Oxidase Activity, and Uric Acid, and Uric Acid Excretion in Human Subjects C-21

CHAPTER 1

The Agricultural Drainage Water Problem: Scope and Limitations of Public Health Analyses

In 1983, waterfowl deaths, deformities, and reproductive failures were discovered at Kesterson Reservoir, a series of man-made ponds designed to receive agricultural drainage waters from parts of the Westlands Water District in the western San Joaquin Valley. These abnormalities apparently resulted when high-selenium soils were irrigated for agricultural use and the resulting selenium-laden drainage waters were transported to the reservoir through the San Luis Drain. Natural evaporation processes in the ponds tended to increase selenium (and other element) concentrations within the reservoir. More importantly, selenium was accumulated by certain plants and fish in the environment to concentrations 2-3 orders of magnitude above that found in the inflow drainage water (a process known as "bioaccumulation"). Thus, through a combination of events, wildlife in the local area were exposed to levels of selenium far greater than otherwise would be anticipated. Investigations throughout California and other western states have indicated that concentrations of selenium and other elements (e.g., arsenic, boron, chromium, and molybdenum) in drainage waters were frequently elevated, either as a consequence of natural water conditions or through mobilization of elements from irrigated soils. In many cases, these concentrations exceeded water quality standards set to protect agricultural crop, wildlife, or human health.

Although drainage waters are not expected to be consumed by humans directly, various pathways exist for human exposure to these waters. As such, assessment of potential public health problems resulting from drainage water contamination and, if necessary, development of intervention plans have been identified as important areas of study in the San Joaquin Valley Drainage Program (SJVDP). In 1987, a Cooperative Agreement between U.S. Bureau of Reclamation (USBR) and the Health Officers Association of California (HOAC) was initiated to begin investigating such issues for the SJVDP. The thrust of this Cooperative Agreement has been to (1) coordinate public health activities with the SJVDP Program Manager, the SJVDP Interagency Technical Advisory Committee (ITAC), and the ITAC Public Health Subcommittee, (2) participate in public meetings in support of the health activities for the SJVDP, (3) identify appropriate interagency problems and provide early warning regarding sensitive issues or unresolved problems, (4) prepare a report summarizing the current state of knowledge relating to agricultural drainage water contaminants as they relate to public health, and (5) provide recommendations for further public health investigations.

For most cases, drainage water contaminants are being studied by the SJVDP because of possible threat to agricultural crops or wildlife in the San Joaquin Valley. It has been the task of this project to evaluate these contaminants for their potential impact on public health. For this report, information regarding the occurrence, environmental fate, essentiality/ biological function, toxicokinetics, toxicity, treatment for overexposure, typical exposure limits, and indicators of excessive exposure has been collected from the scientific literature for each of the drainage contaminants that have been considered of greatest concern by state and federal agencies; i.e., selenium, boron, and molybdenum (see Appendices A, B, and C). This information, along with data collected from the SJVDP study area (Figure 1), has been used to assess the likelihood of human exposure to drainage contaminants from a number of potential exposure routes (see chapters 4, 5, and 6). Additionally, data from the scientific literature regarding health outcomes following known exposures to these elements have been collated for future comparison to San Joaquin Valley-specific exposure information. Where appropriate, inferences have been made concerning the current potential for public health risk from exposure to individual trace elements in agricultural drainage waters.

As with any biological situation of this complexity, certain caveats must be stipulated to mitigate the possibility of misinterpretation of report data and conclusions. First, the appendices are not intended to be original, comprehensive reviews of the literature for each of the elements under investigation. The information presented in the appendices is based in large part on the data and opinions of experts in the respective fields of selenium, boron, or molybdenum nutrition and toxicology. Additionally, these appendices and public health reviews (chapters 4, 5, and 6) have been designed to provide information that is deemed necessary for the formulation and evaluation of alternatives by the SJVDP and may not be useful for situations occurring outside the drainage study area.

Second, public health reviews do not address the potential consequences of occupational exposures to drainage contaminants, such as might occur during hazing or clean-up operations in highly contaminated sites like Kesterson Reservoir.

Third, at this time, public health reviews of the potential risk from exposure to various drainage contaminants assume a certain normality of consumption and behavioral patterns in the local population. For example, it is assumed (in keeping with various federal estimates) that the vast majority of persons consume 2 liters or less of water per day. Thus, the value of 2 liters/day is used to calculate the dietary contribution of water for a given element from a given water source with known concentration of that element. Gross deviation from norms of dietary or behavioral patterns (e.g. disproportionate consumption of produce from home gardens in the Panoche Fan area or gathering and disproportionate consumption of wild plants, fish, and wildlife from the Valley trough) may invalidate the perceived risk from exposure to a particular source of drainage contaminants.

Fourth, interactions between drainage contaminants or other confounding variables have not been considered when assessing potential public health risk from exposure to any individual element. Known interactions between elements that may affect the availability of a given contaminant (such as arsenic and selenium) or confounding factors that may exacerbate the toxicity of a given contaminant (such as dietary protein deficiency and selenium toxicity) have been described in the individual appendices. Understanding of these interactions or knowledge regarding the populations at risk is not sufficient to be incorporated into public health reviews.

Fifth, it is important to note that many of the drainage contaminants currently under investigation by the SJVDP are required nutritionally for humans and animals. Thus, exposure to adequate levels of these elements is necessary and desirable.

Sixth, this report represents evaluation of the drainage water situation in the western San Joaquin Valley given present knowledge. The information used to assess potential public health exposures to drainage contaminants has

San Joaquin Valley Drainage Program Study Area

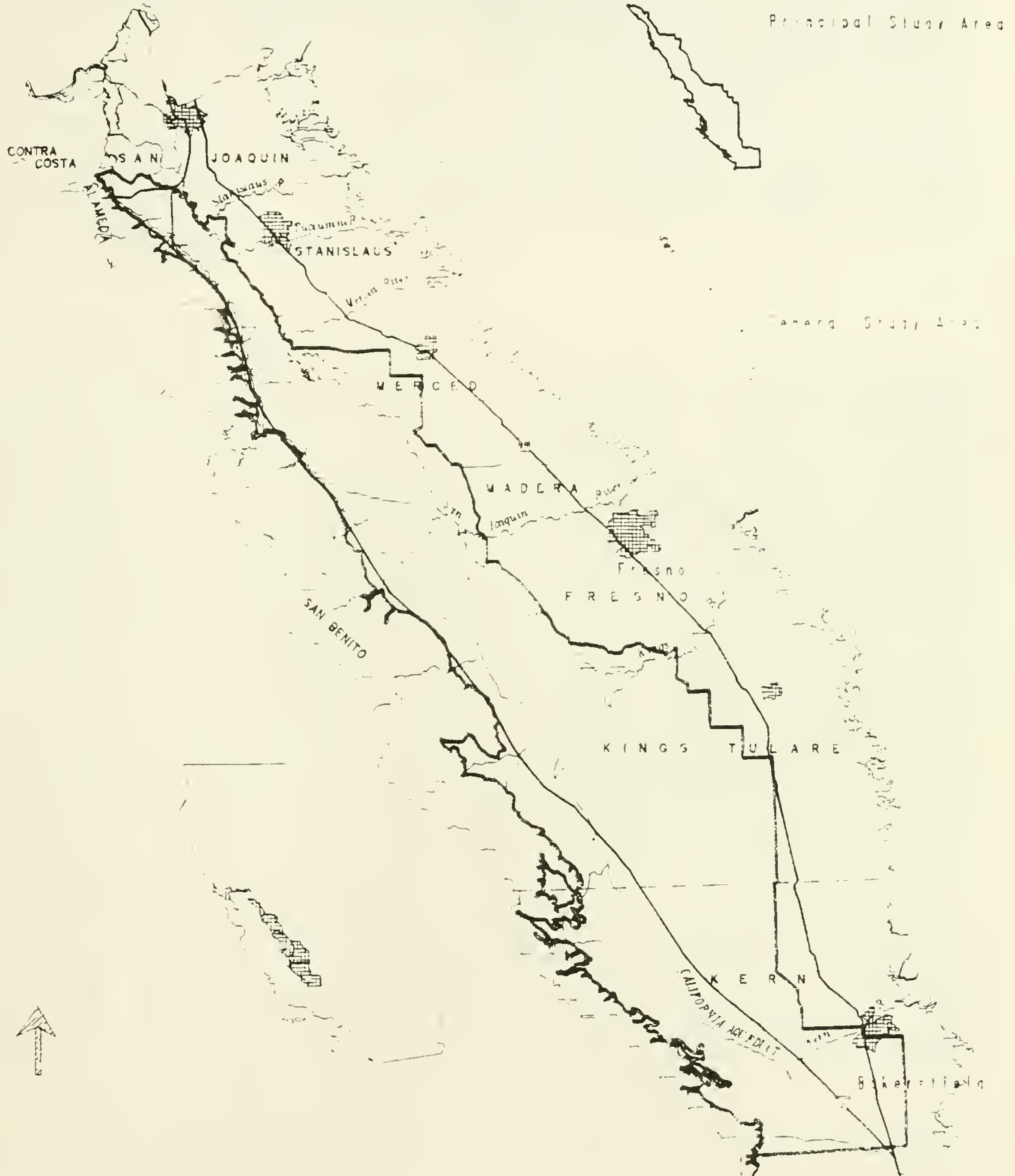


Figure 1

been obtained from many sources (see chapter 3) which, while deemed reliable, have not been collected under the control of the authors and, in most cases, have not been accumulated for the purposes of public health assessments. New information ascertained in the coming months and years may cause reevaluation of agricultural drainage water contamination as it relates to public health. Additionally, these reviews are based on current conditions in the San Joaquin Valley; changes in agricultural drainage water management or treatment may invalidate the findings of this report.

CHAPTER 2

Previous Public Health-Related Studies in the San Joaquin Valley

Few studies have been conducted in the western San Joaquin Valley for the sole purpose of investigating the public health impact of agricultural drainage water contamination. Some studies have been designed to evaluate occupational exposures for Kesterson Reservoir workers, and other studies, while not directly related to public health, may be useful for assessing human exposures to drainage contaminants. The following are descriptions of data previously obtained from the study area that have been used to formulate the need and scope of the present document.

Public Health Studies and Assessments

Almost immediately after reports of wildlife deaths and deformities in Kesterson Reservoir, the Merced County Health Department initiated a survey of possible health problems in a population presumed at risk for exposure to drainage contaminants. Kesterson area residents were compared to age- and sex-matched controls from a nearby community (Gustine); a medical history questionnaire was administered; and blood chemistry panels as well as several toxicological analyses were performed. Although the study was limited in scope, evidence was not found to indicate that adverse health effects resulting from proximity to Kesterson Reservoir were occurring. However, the Merced County Health Department recommended further study, including the collection of additional data, and establishment of procedures to validate initial findings and to assure continued health protection of local residents.

The health status of Kesterson National Wildlife Refuge personnel (employees of the U.S. Fish and Wildlife Service and the U.S. Bureau of Reclamation) has been monitored since October, 1984. The occupational health program for employees has included regular (every 3 to 4 months) blood chemistry analyses and selenium measurements in blood and urine. Symptoms indicative of selenium overexposure have not occurred, and selenium biochemical indices have been within normal limits. The monitoring program currently continues. [Refer to Appendix A, Section IX, for a discussion of the value of biochemical indicators of excessive selenium exposure.]

A small ethnographic survey of Southeast Asian populations known to forage for food in the Kesterson area was conducted in 1987 by the University of California Cooperative Extension, Rural Development Program. Preliminary conclusions indicated that Southeast Asians do not consume sufficient amounts of foraged items that selenium overexposure would occur; however, the study design was inadequate to fully test this hypothesis. Additionally, foraging for wild plants or animals may be a practice of other residents of or visitors to the San Joaquin Valley; this has not been investigated.

In 1986, a survey was conducted of Southeast Asian Refugees believed to be foraging foodstuffs in the Kesterson area by Dr. Steven Segerstrom of the Merced Family Practice Residency Program. Eleven families of these families consented to participate in a health questionnaire and blood, urine, and hair collection. Data analyzed were compared to a control population of Laotian patients in the community family practice clinic. Conclusions of this study indicated that adverse effects did not appear to be occurring as a result of excessive selenium consumption in this population. The author recommended further longitudinal studies to investigate selenium consumption patterns during other seasons.

Analyses of Contaminant Levels of Various Exposure Sources

While initial surveys of presumed high risk groups did not yield indications of adverse health consequences related to contaminant exposure, it was recognized by the SJVDP that broader monitoring activities should be conducted. Since 1984, water, air, soil/sediments, and food items have been analyzed by various agencies for elements known to be elevated in agricultural drainage waters, particularly selenium. The following paragraphs are descriptions of studies that are either completed, underway, or planned, and are categorized with respect to major exposure sources.

Water Water that contains excessive levels of elements, minerals, or other compounds may adversely affect public health either directly, through ingestion or dermal absorption of these substances, or indirectly, through contamination of human food (e.g., wildlife, crops, or livestock). Current federal guidelines for selenium in water are 10 ppb for human consumption and 20 ppb for irrigation. Water quality is monitored throughout California by state and federal agencies for research and regulatory purposes. These data are available to the SJVDP for analysis and interpretation related to the agricultural drainage problem. In the study area, isolated ground and surface waters have been found to contain exceedingly high (over 500 ppb) selenium levels. These concentrations usually have been found in association with agricultural drainage sumps or collector drains and would typically be diluted very quickly by the merging of sump water with other, higher quality water. The U.S. Geological Survey (USGS) has reported selenium concentrations up to 28 ppb in Mud and Salt Sloughs (which drain high-selenium agricultural lands), and generally lesser concentrations in other rivers and streams throughout the San Joaquin basin. Other elements (including boron, molybdenum, chromium, and arsenic) have also been found to exceed recommended water quality criteria.

In addition to inorganic minerals, organic chemicals (e.g., pesticides) are also monitored in various waters throughout the state. Under the Pesticide Contamination and Prevention Act (AB 2021), the California Department of Food and Agriculture (CDFA) is required to prepare annual reports to the Legislature regarding pesticides in drinking water from ground water sources. According to the first annual report (1986), very low levels of organic residues have been found in well waters in large parts of the SJVDP study area, particularly in Fresno and Merced Counties. Most often detected are dibromochloropropane (DBCP) and ethylene dibromide (EDB), two pesticides that have been banned for use in recent years. Because subsurface agricultural drainage water is often mixed with surface drainage (tail water), the SJVDP has considered the initiation of a project to assess the potential impacts of pesticides in agricultural drainage waters and receiving waters.

Air Air quality monitoring activities that have been conducted at Kesterson Reservoir serve to measure particulate selenium exposures in reservoir employees. Sampling and analysis at the reservoir and surrounding areas were initiated in 1985 and have continued to date, in cooperation with the California Air Resources Board and the Pollution and Control Districts of Merced and Fresno counties. Results of air quality data are compiled in the USBR Kesterson Program EIS report (1986) and indicate that ambient air in and around Kesterson Reservoir does not contain sufficient particulate selenium to be considered a potential human health threat.

A proposed technique for treatment of high-selenium soils and vegetation is to dramatically increase natural volatilization of gaseous selenium metabolites by cultivation of natural soil microorganisms (especially fungi) through addition of organic material. The predominant form of selenium released during this process is believed to be dimethylselenide. Because the toxicity of inhaled dimethylselenide is not well characterized, studies have been initiated at the University of California - Davis to investigate this issue.

Food Fruits, nuts, vegetables, and various domestic animal products have been analyzed to determine trace element concentrations. Because of the concern of bioaccumulation of trace elements in food items, CDFA surveyed animal and animal products under a contract to the U.S. Bureau of Reclamation (USBR). Although data were limited, the ensuing report concluded that, based on available data, consumption of domestic animals or animal products originating from the study area should not pose a public health risk. Similarly, a University of California Agricultural Issues Center report, based on preliminary data collected by the UC Salinity Drainage Task Force, indicated that agricultural fruits, nuts, and vegetables have not accumulated dangerous selenium concentrations. Continued monitoring is recommended.

The U.S. Fish and Wildlife Service (USFWS) provides analytical findings that can be used for assessment of public health risks from exposure to animals in the drainage area. USFWS conducts two types of studies: (1) surveys to determine contaminant levels in field conditions (e.g., selenium concentrations in duck livers), in cooperation with the California Department of Fish and Game and the California Department of Water Resources and, (2) laboratory toxicity testing (e.g., to ascertain what level of selenium in water causes toxicity in animals), in cooperation with the University of California. Analyses are performed to determine the toxicological impact of various contaminants on the animals themselves and, thus, results are not usually directly applicable to human consumption (e.g., analyses are frequently conducted on liver tissue instead of muscle tissue that would be consumed more frequently by humans). However, this does afford estimation of a worse-case scenario regarding ingestion of such animals. Soil and vegetation analyses of various elements are also conducted in an attempt to assess the extent of contamination in an area and the bioaccumulation factor (BAF) for a given element in a given species. Information gleaned from the above, and other, studies has resulted in the issuance of health advisories from the Merced County Health Department, the California Department of Health Services (CDHS), and the California Department of Fish and Game (CDFG) to limit consumption of fish and wildlife from Kesterson Reservoir, wildlife from the Grasslands area, and fish or coots from irrigation/evaporation ponds in northwestern Kern County and southwestern Kings County. Warning signs and advisories have been posted in the areas advising of such restrictions.

Preliminary assessments by CDHS have indicated that consumption of agricultural crops and domestic animals grown or raised in the drainage area does not appear to increase the level of selenium intake in adults and children beyond that considered safe and adequate. These results are only provisional, however, and further analyses are required (for selenium and other elements), under varied conditions, before a complete assessment can be provided.

Soil and Sediments Humans may be exposed to contaminants in soil and/or sediments through dermal contact, or occasionally, ingestion (e.g., hand-to-mouth contact in children). The extent of selenium (or other element) absorption in humans via these routes is unknown in non-industrial settings. Indirectly, contamination of soil and sediments may lead to increased uptake of these contaminants by plants or animals that subsequently may be consumed by humans. Additionally, leaching of elements in soil or sediments can contaminate region ground water aquifers used to supply drinking water. USBR, USFWS, and USGS have evaluated soil and sediments in the drainage area; however, their studies have not been conducted for the purpose of assessing potential public health risk of contact with these substances.

CHAPTER 3

Sources of Data for Current Health Assessments

In the following three chapters, numerous sources of information have been used to assess potential public health exposures to agricultural drainage contaminants. Much of the data have been collected by state and federal agencies in association with the San Joaquin Valley Drainage Program; additional data have been collected by the University of California (UC)-Salinity/Drainage Task Force, the California State Water Resources Control Board (SWRCB) and California Department of Fish and Game (CDFG) Selenium Verification Study, and the U.S. Department of Interior National Irrigation Drainage Program. The following discussion presents information sources for each of the exposure media, including usefulness of the data for public health assessments.

FISH AND WILDLIFE DATA:

Biological Residue Data Base

A principal source of information regarding contaminant concentrations in various fish and wildlife in the drainage study area is the Biological Residue Data Base (Biores Data Base) developed by the USFWS in conjunction with the SJVDP. Information compiled in this data base includes a reference number of the study, the location or site name where the samples were obtained, the taxon and species, the contaminant and tissue sampled, the sample date and size, the mean contaminant concentration in the sample(s) analyzed, the minimum and maximum concentrations measured in the sample(s), and whether the sample was measured on a wet- or dry-matter basis. This data base primarily includes summary figures from published information. Currently, the Biores Data Base contains approximately 2,700 records. Sampling sites throughout the Valley have been mapped and will soon be digitized, tying this data base with the SJVDP-developed Geographic Information System (GIS).

Because these data have been collected primarily for the assessment of food chain contamination and effect on fish and wildlife, there are several disadvantages to the use of this information for public health assessments. First, analyses frequently have been made on tissues that are not typically consumed by humans. For example, in many cases whole fish (including bones, heads, and tails) or fish livers have been used for contaminant analysis. Extrapolation of these values to edible tissues is difficult. Because better data are not available, for the purpose of this report it generally has been assumed that whole organism concentrations may be reasonably reflective of edible (muscle) tissue concentrations; muscle tissue contaminant concentrations likely do not exceed those measured in the whole organism. Because liver tissue tends to accumulate many elements to a higher degree than do other tissues, liver concentrations of contaminants are usually considered a "worst case" human exposure.

Second, the data base includes values as reported. Contaminant analyses are usually made on dry samples; thus, for determination of human exposures, sample contaminant concentrations must be converted to fresh weight (as consumed) basis. Frequently, fresh weights or percent moisture values are not available for each sample and the original data must be obtained or a standard conversion factor used. This introduces additional error into any calculation of exposure.

Third, many of the species analyzed are not consumed by humans. Plants such as green algae, widgeongrass, and cattails; invertebrates such as water boatmen and damselfly nymphs; fish such as mosquitofish and fathead minnows; and birds and mammals such as killdeer, swallows, shrews, and mice comprise a significant portion of the data base. These data are useful for examining wildlife exposures or determining bioaccumulation factors, but are not valuable for assessing human exposures.

Fourth, many of the sample sizes are either very small or not reported. Additionally, some values were expressed as geometric means and others as arithmetic means. As such, we reported a range of means for each study as well as the highest value reported for each species (to estimate the "worst case" exposure) (see chapters 4, 5, and 6). As some of these high values were high means, this may lead to an underestimation of exposure to an element from a particular source in some geographic areas and an overestimation of exposure to an element in other areas.

In general, with the exception of the above constraints, the Biological Residue Data Base is a very useful compilation of data for examination of contaminant levels in fish and wildlife in the western San Joaquin Valley. This data base is being continually updated with new information and may be accessed by contacting:

Stephen B. Moore
Drainwater Studies Coordinator
U.S. Fish and Wildlife Service
San Joaquin Valley Drainage Program
2800 Cottage Way, Room W-2143
Sacramento, CA. 95825
916-978-4969

Selenium Verification Study

The Selenium Verification Study began in 1985 by CDFG for the SWRCB. The study has been conducted statewide, including several areas in the western San Joaquin Valley. These data are useful for assisting in the determination of human selenium exposures in the drainage study area. For this project, the Selenium Verification Study - 1986 Report (released in May, 1987) was used; however, additional study results (not used for this project) were released by the SWRCB in February, 1988. As an additional component of the Selenium Verification Study, the University of California - Davis, Veterinary Diagnostic Toxicology Laboratory has been conducting analyses to detect the concentrations of twenty other elements (including arsenic, boron, cadmium, chromium, copper, mercury, molybdenum, and zinc) in fish and wildlife throughout the state. This work was released by the SWRCB in late Spring, 1988.

For this document, data from the San Joaquin River at the Merced River, Salt Slough, Mud Slough, Camp 13 Ditch (South Grasslands), Tulare Lake Drainage District, Twisselman Road (Westfarmers evaporation ponds), Lost Hills Ranch evaporation ponds, and the Semitropic Water Storage District ponds were evaluated. Only data obtained from fish and wildlife reported to be used as human food sources were included.

Unlike the Biological Residue Data Base, most of the sample concentrations in the Selenium Verification Study are reported on a wet-weight basis. Additionally, concentrations in edible tissue are usually provided along with a diagram and description of the dissection technique. The Selenium Verification Study also provides a discussion of the species of fish or wildlife sampled in each of the collection areas, including feeding and migratory patterns, reproductive habits, and the probability of their use as game by hunters.

Sample size is also fairly small in the Selenium Verification Study; results were reported as ranges for each geographic area (see chapter 4).

The Selenium Verification Study is a very useful document for obtaining selenium concentrations in selected fish and wildlife in limited regions of the drainage study area. Because of the manner in which these data have been collected and presented, they are particularly helpful for public health assessments. Information regarding the Study can be obtained from:

Dale A. Watkins
Environmental Specialist
Agricultural Drainage
State Water Resources Control Board
P.O. Box 2000
Sacramento, CA. 95810
916-324-5674

AGRICULTURAL CROP AND DOMESTIC ANIMAL DATA:

U.S. Salinity/Drainage Task Force, Technical Progress Reports, 1985-1986 and 1986-1987. Division of Agriculture and Natural Resources, University of California. U.C. Salinity/ Drainage Task Force, Special Publication [in press].

The UC Salinity/Drainage Task Force was initiated in January, 1985 to address the problems of agricultural drainage in the state of California. In July, 1985, a $1.05 million research program was begun through a competitive grant process. In September, 1986 and October, 1987 technical progress reports of the funded research projects were distributed. These progress reports include the project title, the source of funding, the duration of funding, the project investigators, the research staff, project collaborators, an abstract, project objectives addressed, research plan and procedures, results, and discussion and summary.

The projects funded by the UC Salinity/Drainage Task Force are varied and frequently basic in nature. They are most useful for understanding the scientific principles behind drainage contamination, mineral uptake into crops, bioconcentration of contaminants in the aquatic food-chain, etc. The Special Publication document [in press] will contain some additional information that is more directly applicable to the determination of public health risk from exposure to drainage contaminants. The most useful information in that regard are reports by Richard Burau et al., that provide selenium concentrations in western San Joaquin Valley food crops; Anna Fan and Ben Norman, that estimate human exposures to bovine liver selenium; and Anna Fan, that calculated the accumulation of selenium in melons, cauliflower, celery, and tomatoes, and selenium concentrations in nut tissues. These are cited in chapter 4.

Copies of the UC Salinity/Drainage Task Force reports may be obtained by contacting:

Kenneth Tanji
Assistant Director
Agricultural Experiment Station
127 Veihmeyer Hall
University of California
Davis, CA. 95616
916-752-8255

Selenium Survey in Animals and Animal Products. California Department of Food and Agriculture, Division of Animal Industry, Bureau of Animal Health. February, 1986.

Blood, milk, liver, wool, and hair samples were obtained from beef and dairy cattle, goats, horses, sheep, and pigs within and nearby to Kesterson National Wildlife Refuge and analyzed for selenium concentration. Control dairy and beef herds from low-selenium regions were used to compare blood selenium values. [Note the value of biochemical indicators of excessive selenium exposure in Appendix A, Section IX.] Estimates for human consumption of these products was also provided.

This report provides useful information for assessing the concentrations of selenium in bovine liver and milk in a small number of samples in the Kesterson area. This report was prepared under contract to the U.S. Bureau of Reclamation and may be obtained from:

Edwin Lee
San Joaquin Valley Drainage Program
2800 Cottage Way (Room W-2143)
Sacramento, CA. 95825
916-978-4969

HUMAN EXPOSURE DATA:

Selenium and Human Health Implication in California's San Joaquin Valley. 1988. Fan, A.M.; Book, S.A.; Neutra, R.R.; and Epstein, D.M. J. Toxicol. Environ. Hlth. 23:539-559.

This paper provides an evaluation of the human health impacts from exposure to selenium in and around Kesterson Reservoir. Selenium concentrations in fish, aquatic birds, waterfowl, animals, drinking water, soil, and air were analyzed for their potential to cause negative impacts on human health. Additionally, blood and urine selenium levels in Kesterson workers were presented.

This report provides an excellent compilation of information related to the potential health risk of selenium exposure to occupational workers and individuals living nearby Kesterson Reservoir. This reported may be obtained from:

Anna Fan, Ph.D.
Staff Toxicologist
Community Toxicology Unit
Department of Health Services
2151 Berkeley Way, Room 619
Berkeley, CA. 94704
415-540-3066

WATER AND SOIL DATA:

U.S. Bureau of Reclamation, Water Quality Analyses. West Side - San Joaquin Valley, July, 1987.

The U.S. Bureau of Reclamation report on water quality analyses in the west side of the San Joaquin Valley provides data that are useful for public health assessments. Water quality data have been collected from (1) domestic well sites in the vicinity of Kesterson Reservoir, (2) Kesterson Reservoir surface water sites, (3) groundwater sites in the vicinity of Kesterson Reservoir, (4) northern Grassland Water District sites, (5) San Luis Drain checks, (6) Kings County sites, and (7) westside creeks. Water quality has been determined in canal water, collector drains, creek water, domestic wells, farm drain sumps, observation wells, ponds, weirs between ponds, the San Luis Drain, and various surface water sources.

For the purpose of public health analyses, data from canals, creeks, and surface waters were used primarily for determination of possible dermal exposures. While it cannot be ruled out that these waters would ever be consumed by humans, it is not considered likely that these waters would be a regular source of significant water intake for any individual. Domestic well water is assumed to be consumed by humans in the quantity of 2 liters/day/person.

Water quality analysis has included determination of electrical conductivity and arsenic, boron, cadmium, chromium, copper, iron, lead, manganese, mercury, molybdenum, nickel, lead, selenium, silver, and zinc concentrations. Suspect data points (those that are possibly the result of analytical error) are clearly marked.

In general, these data are very useful for determining the concentrations of a large number of elements in some waters in the Kesterson area to which humans may have access. Water samples are collected and analyzed on a regular basis so that temporal trends may be taken into consideration. Only a small number of domestic wells are included in the survey; however, surface water sources (canals, creeks, and sloughs) are well represented in the report. This data base may be accessed by contacting:

John Fields
Physical Scientist
U.S. Bureau of Reclamation
2800 Cottage Way, Room W-2103
Sacramento, CA. 95825
916-978-5581

U.S. Geological Survey, Selected Water-Quality Data for the San Joaquin River and its Tributaries, California, June to September, 1985. Open-File Report 86-74.

This survey of water quality in the San Joaquin River and its tributaries was conducted by the U.S. Geological Survey (USGS) in the summer of 1985 to determine the impact of agricultural drainage water on the river, delta, and San Francisco Bay. Eleven sites on the river and its tributaries were selected for evaluation; analyses conducted included streamflow, specific conductance (an indirect measure of dissolved solids), dissolved solids, and total and dissolved concentrations of selenium, boron, and molybdenum. Samples were collected 2 or 3 times monthly for 4 months.

For the purposes of the public health document, the San Joaquin River near Stevinson, Salt Slough near Stevinson, the San Joaquin River at Freemont Ford, and Mud Slough near Gustine were chosen at the most likely sites to contain elevated levels of trace elements. These data are useful for determination of possible human exposures to specific trace elements in certain surface water sources in the western San Joaquin Valley. This report may be obtained from:

U.S. Geological Survey or
San Joaquin Valley Drainage Program
2800 Cottage Way
Sacramento, CA. 95825
916-978-4643
916-978-4969

Dissolved-Selenium Data for Wells in the Western San Joaquin Valley, California, February to July, 1985. Open File Report 86-73.

The USGS conducted a water quality survey from February to July 1985, to determine the concentrations of dissolved selenium in 63 wells in the western San Joaquin Valley. Wells from both the unconfined and confined aquifers were sampled. Wells were characterized as to their primary use: general agriculture; commercial; domestic; irrigation; industrial; public supply; dewatering; and unused. These data are useful for evaluation of the selenium concentration in domestic water supplies in the western San Joaquin Valley. The report may be obtained from:

U.S. Geological Survey or
San Joaquin Valley Drainage Program
2800 Cottage Way
Sacramento, CA. 95825
916-978-4643
916-978-4969

Water-Quality Data, San Joaquin Valley, California, 1985-1987, USGS Open File Report (in press).

The USGS has conducted water-quality analyses from the Tulare Basin region in domestic and agricultural wells. Information reported in this document (currently subject to revision) includes the well number, station number, date, time, depth of well, elevation of land surface, specific conductance, pH, temperature, hardness, dissolved solids, alkalinity, carbon dioxide, sulfate, as well as concentrations of the elements calcium, magnesium, sodium, potassium, chloride, fluoride, bromide, iodide, silica, nitrogen, phosphorus, carbon, aluminum, arsenic, barium, boron, cadmium, chromium, copper, iron, lead, lithium, manganese, mercury, molybdenum, nickel, selenium, silver, strontium, vanadium, and zinc.

These data are quite useful for assessing possible human exposures to many elements in water and may be obtained (when finalized) from:

Molly Welker
Hydrologist
USGS District Office
Water Resources Division
Room W-2234
2800 Cottage Way
Sacramento, CA. 95825
916-978-4648

Kriging Techniques Applied to Element Distribution in Soils of the San Joaquin Valley, California. 1986. Tidball, R.R.; Grundy, W.D.; and Sawatzky, D.L. In: Proc. Haztech International Conference. Denver, CO. August 11-15, pp. 992-1009.

This paper provides maps of selenium and mercury concentrations in San Joaquin Valley soils. This paper is useful for determination of regional distribution of soil element levels so that regions with the highest crop element concentrations may be estimated. This paper is available from:

Walter Swain
Hydrologist
U.S. Geological Survey
San Joaquin Valley Drainage Program
2800 Cottage Way
Sacramento, CA. 95825
916-978-4969

CHAPTER 4

Public Health Review of Data and Data Gaps for Selenium in the Western San Joaquin Valley

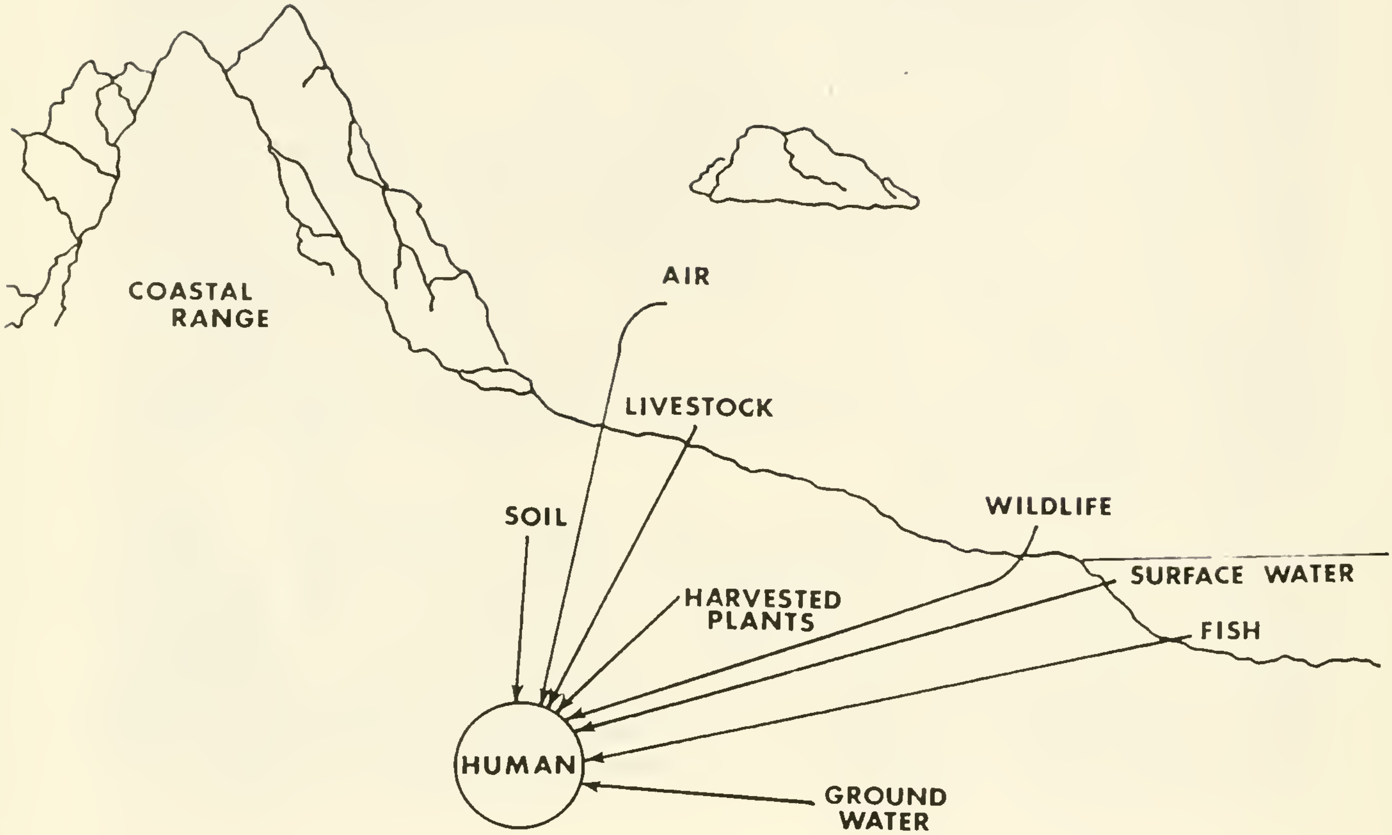
In almost any geographic area, various forms of selenium (Se) will be found at some concentration in air, ground water, surface water, soil, plants, and animals. In some regions, Se levels found in one or more of these different sources may be much higher than national norms; these areas are called "seleniferous". Because of their geologic origin, soils in certain isolated pockets in the coastal range and western San Joaquin Valley of California may be considered seleniferous. Some ground waters in these areas have also been found to contain naturally elevated levels of Se. In recent years, agricultural production expanded into some seleniferous regions of the western San Joaquin Valley. As is the case with many other agricultural areas in the state, irrigation of the land was required and subsurface drains were installed to collect and remove shallow ground water. These Se-laden waters were subsequently transported, either directly or via various canals and ditches, to the San Luis Drain, and finally, into Kesterson Reservoir or through the Grassland Water District en route to the San Joaquin River. Surface water, sediments, plants, and some fish and wildlife in Kesterson Reservoir acquired Se levels much greater than would be expected in areas far removed from the original seleniferous region.

Figure 2 depicts various routes of human exposure to environmental sources of minerals in the western San Joaquin Valley, which, individually or together, have been evaluated for their potential contribution to excessive intakes of these minerals. Some of these routes are direct (e.g., consumption of minerals in ground water), while others are indirect (e.g., consumption of foods that have been irrigated with highly mineralized water). The primary routes of exposure are: consumption of wildlife, fish, plants (including agricultural produce), livestock and livestock products, ground water, and surface water, as well as inhalation and dermal absorption of minerals from air, soil, or water.

Importance of Different Se Exposure Routes for Human Populations

A number of sources of data were used to assess the likelihood of exposure to minerals from different exposure routes. These are described in chapter 3. Data from the Biological Residue Data Base, the Selenium Verification Study, and the UC Salinity/Drainage Task Force are presented to provide examples of selenium concentrations in fish and wildlife, some vegetables, and bovine milk and liver tissue from the western San Joaquin Valley (tables 1 and 2). These values were converted to fresh weights using either specific data provided by the study or national averages, when individual fresh weights were not available. Typical portion sizes (per meal; table 3) (Pennington and Church, 1985; Watt and Merrill, 1975) were used to determine the micrograms of selenium provided by each of these products, using the range of mean selenium concentrations for each type of foodstuff and the highest selenium concentration found ("worst case"). [Because of large potential differences among individu-

Figure 2



POTENTIAL HUMAN MINERAL SOURCES

Table 1. Examples of Selenium Concentrations in and Human Exposures from Consumption of Livestock, Fish, and Wildlife in the Western San Joaquin Valley[a]

			Se Concentration (ppm)[c]		Se Exposure (ug/serving)[d]	
Source	Tissue	Geographic Area[b]	Range of means	Maximum	Typical range	"Worst"
Bovine	Milk	A	0.013-0.023	0.041	3.05-5.59	10
	Liver	A	0.2982-0.3522	0.510	29.8-35.2	51
Calif. ground squirrel	Liver	K	0.243-0.546	0.870	24-55.6	87
	Liver	VWA	0.174-0.330	0.33	17-33	33
Cottontail rabbit	Thigh m.	K	0.504-0.528	0.792	50-53	79
	Thigh m.	VWA	0.027-0.029	0.029	2.7-2.9	3
Muskrat	Liver	K,SLO	0.510-9.63	27.6	51-963	2760
	Liver	VWA	0.105-0.570	0.570	11-57	57
American coot	Liver	K	21.3	41.8	2130	4180
	Liver	GWD,VWA,LHR, TLO,STW	0.92-6.70	11.0	92-670	1100
	Egg	K	8.96	21.5	448	1075
	Egg	VWA	0.22	0.32	11	16
	Breast m.	TLD,STW,LHR	0.26-2.50	5.8	26-250	580
Cinnamon teal	Egg	K	2.12-4.19	11.47	106-210	574
	Egg	GWD,VWA	0.65-2.02	2.08	33-101	104
	Breast m.	TLD,STW,LHR	0.58-1.50	2.8	58-150	280
	Liver	TLD,STW,LHR,WF	2.5-5.7	11.0	250-570	1100
Mallard	Liver	GWD	0.99-1.60	3.40	99-160	340
	Egg	K	3.22-4.71	9.61	161-236	481
	Egg	GWD,VWA	0.37-1.13	1.86	19-57	93

Table 1 (cont.). Examples of Selenium Concentrations in and Human Exposures from Consumption of Livestock, Fish, and Wildlife in the Western San Joaquin Valley[a]

Source	Tissue	Geographic Area[b]	Se Concentration (ppm)[c]		Se Exposure (ug/Serving)[d]	
			Range of means	Maximum	Typical range	"Worst"
Black bullhead	Whole	MS	1.7-2.5	2.5	170-250	250
Bluegill	Whole	MS,VW,SJR,SS,HC	0.22-4.60	4.60	22-460	460
Channel catfish	Whole	CD	0.95-1.20	1.20	95-120	120
	Whole	SLD	13.5	17.0	1350	1700
	Muscle	SJR,SS,MS,CD	0.24-0.75	0.90	24-75	90
	Liver	SJR,SS,MS,CD	1.7-2.6	2.6	170-260	260
Common carp	Whole	SLD	34.3	60.0	3430	6000
	Whole	AC,HC,SJR,SLC, CD,LB,MS,SS,VWA	0.08-3.79	3.79	8-379	379
Green sunfish	Whole	SS,HC,MS,LB, GWD,CD,MC	1.2-5.5	5.5	120-550	550
Sacramento blackfish	Whole	SLD	16.2	33.0	1620	3330
	Whole	CD,HC,LC,SS,SJR	0.18-3.9	3.9	18-390	390
Striped bass	Whole	LB,MS,SS,VW, MC,SJR,HC	0.30-2.27	2.35	30-227	235
White catfish	Whole	MS,LB	0.37-1.30	1.30	37-130	130
	Muscle	SS,SJR	0.20-0.29	0.34	20-29	34
	Liver	SS,SJR	1.5-2.5	2.5	150-250	250

Table 1 (cont.). Examples of Selenium Concentrations in and Human Exposures from Consumption of Livestock, Fish, and Wildlife in the Western San Joaquin Valley[a]

Source	Tissue	Geographic Area[b]	Se Concentration (ppm)[c]		Se Exposure (ug/Serving)[d]	
			Range of means	Maximum	Typical range	"Worst"
Yellow bullhead	Whole	PC,GLC	0.344-0.387	0.452	34.4-38.7	45
Bent clam	Muscle	MS	0.50	0.50	50	50
Freshwater clam	Muscle	SFC,CD,MS, SS,VWA	<0.2-4.0	4.0	<20-400	400

[a] Data were obtained from the Biological Residue Data Base and the Selenium Verification Study (see Chapter 3).

[b] A, bordered by Fresno Slough and San Joaquin River on the east, I-5 on the west, Fresno-Kings County line on the south, and San Joaquin County on the north; AC, Agatha Canal; CD, Camp 13 Ditch; GLC, Goose Lake Canal; GWD, Grassland Water District; K, Kesterson Reservoir; LB, Los Banos Creek; LHR, Lost Hills Ranch; MC, Main Canal; MS, Mud Slough; PC, Poso Creek, Kern Co; SFC, Sante Fe Grade Canal; SJR, San Joaquin River; SLC, San Luis Canal; SLD, San Luis Drain; SS, Salt Slough; STW, Semitropic Water Storage District Ponds; TLD, Tulare Lake Drainage District Ponds; VWA, Volta Wildlife Area; WF, Westfarmers Evaporation Ponds.

[c] Concentrations are based on fresh weights; fresh weight conversion factors were obtained from either the respective studies or Pennington and Church, 1985.

[d] Exposures are based on intake (ug) per serving; typical serving sizes are listed in Table 3.

Table 2. Examples of Selenium Concentrations in and Human Exposure from Consumption of Agricultural Crops in the Western San Joaquin Valley[a]

Source	Tissue	Sample Size	Se Concentration (ppm)[b] Geometric mean	Se Concentration (ppm)[b] Maximum	Se Exposure (ug/serving)[c] Average	Se Exposure (ug/serving)[c] "Worst"	Se Exposure (ug/serving)[c] U.S. Average[d]
Bell pepper	Fruit	9	0.0078	0.0132	0.78	1.32	
Broccoli	Head	14	0.0530	0.1106	5.30	11.06	
Cabbage	Head	30	0.0136	0.0281	1.36	2.81	2.2
Cantaloupe	Fruit	9	0.0128	0.0303	2.05	4.85	0.4
Carrot	Root	4	0.0407	0.0652	4.07	6.52	2.2
Cauliflower	Head	15	0.0385	0.0877	3.85	8.77	0.6
Corn	Grain	7	0.0036	0.0328	0.58	5.25	0.4
Garlic	Root	4	0.0381	0.0739	3.81	7.39	24.9
Lettuce	Head	6	0.0023	0.0081	0.23	0.81	0.8
Lima bean	Seed	5	0.0685	0.0796	6.85	7.96	
Onion	Bulb	5	0.0070	0.0082	0.70	0.82	1.5
Sugar beet	Root	5	0.0030	0.0068	0.30	0.68	
Tomato	Fruit	12	0.0034	0.0072	0.34	0.72	

[a] Data were obtained from Burau et al., 1988.

[b] Se concentrations are based on fresh (wet) weight; fresh weight conversion factors were obtained from Pennington and Church, 1985.

[c] Exposures are based on intake (ug) per serving; typical serving sizes are listed in Table 3.

[d] National averages were obtained from Pennington and Church, 1985.

Table 3. Portion Size Averages for Exposure Estimates.*

Milk - one 8 oz. glass (244 g)
Liver, breast muscle, or whole animal - 3½ oz. (100 g)
Egg - one egg (chicken size ~ 50 g)
Clam - 4 to 5 large clams (~ 100 g)
Bell pepper - 1 large
Broccoli - 1 stalk
Cabbage - 1 cup shredded
Carrot - 1 large
Cauliflower - 1 cup pieces
Lettuce - 3½ ounces
Lima Beans - 5/8 cups .
Onion - 1 medium
Tomato - 1 small
Cantaloupe - 1 cup
Corn - 5½ inch ear

---

*Average portion sizes were obtained from Pennington and Church, 1985; Watt and Merrill, 1975.

als, national averages concerning typical portion sizes, edible portions, etc., must be interpreted with caution.] Data for fish and wildlife were reported according to geographic location; Kesterson Reservoir and San Luis Drain data are reported independently.

In the case of many food items, some national averages for nutrient concentrations are provided by various publications, including the 14th Edition of Food Values of Portions Commonly Used (Pennington and Church, 1985). Where available, national averages for selenium concentrations of foodstuffs have been included to provide comparison values to that of local products (see table 2). It is important to note, however, that because of wide geographic variability as well as inconsistencies in different analytical methodologies, national trace element averages may not be reliable (Pennington and Church, 1985).

Information from the scientific literature also has been used to evaluate the relative availability of selenium from different exposure routes. This is especially important in cases where a particular exposure route may strongly influence the rate of selenium absorption. This information is more fully described in Appendix A.

Based on the information above, exposure routes have been ranked for their potential contribution to exposure of humans to Se in the local area and are discussed in the following pages and summarized in table 4. It is important to note, that unless specifically stated, rankings do not necessarily imply concomitant health risk (i.e., a ranking of 3 does not imply a 3-fold greater health risk of exposure from this route than from a route with a rank of 1). The criteria used to rank exposure routes were as follows: a ranking of 1 was used when levels of the element obtained from this route generally were within nationally-expected norms; a ranking of 2 was used when levels of the element routinely were higher than national norms, but the route would not necessarily provide a significant portion of the daily intake; a ranking of 3 was used if the route provided higher than normal levels and would provide a significant portion of the diet; a ranking of 4 was not used, but would be indicated if a route currently was being evaluated for some regulatory or advisory action; a ranking a 5 was used when health advisories limiting exposure via this route were in effect.

Studies of fish and wildlife in the Grassland Water District have indicated that Se has accumulated to such a degree in some areas that consumption of these animals should be limited in the general population or avoided altogether by certain subgroups of the population (e.g., children and pregnant women). Health advisories issued by local authorities and the California Department of Health Services have notified persons entering affected areas of these restrictions. Given present information, these two sources would be considered the most likely routes of Se intake in excess of nutritional requirement, were their ingestion not contraindicated by public health officials. It is possible, however, that birds accumulating hazardous levels of Se in one area could migrate to another area where ingestion is not restricted. Additionally, the degree of public compliance with health advisories is unknown.

Se analyses of agricultural crops in the area have been limited, but, so far, do not indicate a potential health threat for persons consuming commercial produce grown in the western San Joaquin Valley. It has been questioned whether persons practicing subsistence gardening or foraging free-growing vegetation in seleniferous regions may be at greater risk for excessive Se

Table 4. Potential Relative Contribution of Different Routes of Increased Se Exposure in the Western San Joaquin Valley.

Route	Rank	Comments
WC	5	Certain forms of wildlife in the drainage area contain sufficient levels of Se that consumption of these animals, particularly organs which accumulate Se, should be limited.Allowable consumption rates will depend on predicted total dietary Se loads.
FC	5	As is the case with animals, certain fish in the drainage area contain contain excessive Se levels. See comments above for consumption restrictions.
PC	U	Field and laboratory studies of plant Se levels in the drainage area have been limited. Proposed drainage water recycling tech- may increase plant Se levels. Further monitoring of plant Se levels is warranted.
APC	U	Preliminary evidence from bovine milk and liver samples does not suggest excessive Se in these tissues. Sampling has been limited, however, and more data are necessary to assure accepable Se levels in animal products.
GWC	1	Currently, most ground water in the area does not exceed federal drinking water guidelines for Se. With the closure of the San Luis drain, it is possible this situation could change. Ground water Se levels should be closely monitored in the drainage area.
SWC	1	Surface water Se levels outside Kesterson Reservoir and the San Luis Drain generally do not exceed 35 ppb. Direct consumption of this water would probably not adversely impact human health, but could contribute to higher Se levels in fish and wildlife.
BDV	U	Preliminary tests of airborne particulate Se have indicated that levels are in the acceptable range. Concentrations of volatilized Se compounds are largely unknown, however.
DC	UL	Dermal absorption of environmental Se appears to be poor. Hand-to-mouth contact could occur in small children playing in seleniferous soils.

WC = wildlife consumption
FC = fish consumption
PC = plant consumption
APC = animal and animal product consumption
GWC = ground water consumption
SWC = surface water consumption
BDV = breathing dusts and volatilzed compounds
DC = dermal contact

U = unknown
UL= unlikely
1 = least exposure potential
5 = greatest exposure potential

intake. Investigations to date have not been sufficient to completely rule out this possibility; however, preliminary data have not shown cause for alarm (see ethnographic survey, chapter 2). Similarly, analyses of bovine tissues from the drainage area have not shown elevated tissue Se levels. Once again, additional data are necessary to assess completely concentrations of Se existing in local domestic animal products.

Selected ground waters along both sides of the California coastal range have been found to contain Se in levels that exceed Environmental Protection Agency (EPA) drinking or irrigation water standards (currently set at 10 and 20 ppb, respectively). In most cases, these levels are not known to be related to agricultural drainage or other industrial practices and appear to exist naturally. In the western San Joaquin Valley, ground water used for drinking has not been found to exceed drinking water standards, and is therefore presumed not to be a health risk at this time (the highest Se concentration in domestic wells in the Kesterson vicinity was 5 ppb, U.S. Bureau of Reclamation Water Quality Analyses, 1987 [see chapter 3]). However, concern has been expressed that, because of the closure of the San Luis Drain, water containing high levels of Se may begin to percolate down to ground water aquifers and contaminate presently safe drinking water sources. Numerous wells now exist to monitor local drinking water aquifers for such an occurrence.

With the exception of the now closed Kesterson Reservoir and San Luis Drain, surface waters in the study area do not usually exceed 35 ppb Se (U.S. Bureau of Reclamation Water Quality Analyses, 1987 [see chapter 3]). These, and somewhat lower, values have been found in Mud and Salt Sloughs, which drain seleniferous lands. Direct consumption of this water, although not expected, would increase the daily selenium intake of an individual and impinge upon the safety margin for this element. A few canals in Merced County have been found to contain considerably higher Se concentrations on an irregular basis (as high as 100-200 ppb Se) These canals are used interchangeably to move both irrigation and drainage waters and, thus, selenium concentrations may vary 50-fold depending on the date of sampling. Because canal water is not believed to be consumed directly by humans, these waters are not expected to serve as a regular source of Se exposure for human populations. Surface waters in the study area that provide drinking water for municipal uses have not been found to exceed established EPA limits.

Although most surface waters in the drainage area are not used for drinking water, they may provide an important indirect source of selenium exposure in humans. Bioaccumulation of Se may occur in plants or wildlife found in these waters when Se concentrations exceed very low levels. Consumption of such wildlife must be considered a potentially significant source of Se.

Se is naturally volatilized from soil, sediments, plants, and, when consumed in excess, from animals. The predominant form of volatilized Se is believed to be dimethylselenide (see Appendix A). This form is generally considered far less toxic than selenite or selenate; however, this assessment has not been made for the known route of human exposure of this compound, i.e., inhalation. Additionally, toxicity values for dimethylselenide were derived only from acute exposures; effects of long-term, low-level exposures have not been investigated. Anecdotal evidence indicates that inhalation of dimethylselenide may cause pulmonary sequelae known as "rose cold" symptoms; the dose required to elicit such a response is not known (see appendix A). Study of the acute inhalation toxicity of dimethylselenide has recently been initiated by University of California researchers.

Other forms of Se may exist in the air as particulate matter. These forms of Se are considered to predominate in urban (as a result of industrial processes), rather than rural, environments and have not been shown to contribute significantly to the average daily intake of Se. Airborne movement of particulate Se from seleniferous soils could possibly increase Se exposure of nearby residents, but preliminary testing has shown concentrations of airborne particulate Se to be within acceptable occupational limits within Kesterson Reservoir itself (see chapter 2). Presumably, airborne Se concentrations would be lower outside the reservoir because of dispersion. Soil Se concentrations (from which airborne particulate Se is derived) in other seleniferous regions of California (e.g., the Panoche Fan) are generally far lower than those found in Kesterson Reservoir.

Humans may come in dermal contact with Se from soil, water, and air. Very few data exist regarding dermal absorption of selenium compounds; however, most non-industrial forms of Se are believed to be absorbed poorly through intact skin; however, absorption through abraded skin could be somewhat greater (see Appendix A). Dermal exposure to seleniferous soils could lead to increased Se ingestion via hand-to-mouth contact in certain population groups, e.g., small children. Based on maximum soil selenium concentrations outside Kesterson Reservoir and the San Luis Drain (approximately 4 ppm), even daily consumption of a few grams of soil would not increase selenium intake levels significantly in these children.

Human Health Effects of Exposure to Se

Health correlates for different Se exposures are presented in table 5. These examples are referenced and described in more detail in Appendix A. Clearly, some levels of Se intake several-fold above those recommended for safety and adequacy have failed to cause discernible Se toxicity symptoms. Accordingly, there appears to be a safety margin between required levels of Se and those causing overt toxicity that is difficult to exceed by normal dietary means. However, there is the possibility that previously unrecognized effects could result from exposure to Se within this margin. Although negative health outcomes following this range of intake are possible as well, current biomedical research in this area has concentrated on the hypothesized cancer chemopreventive effects of Se, when provided in levels that are in excess of the nutritional requirement. This hypothesis has been supported by animal laboratory research and epidemiological data obtained from humans; human clinical trials are now in progress. Exactly what intake level of Se maximizes health while not imparting negative health consequences remains to be elucidated.

Evidence provided to date would indicate that, under current conditions and providing public adherence to safety guidelines, health risks from excessive Se exposure for persons residing in the western San Joaquin Valley are not occurring. Additional monitoring of selenium concentrations in local food, water, and air, as well as further assessment of special population subgroups who may have unusual exposures to Se will help to assure maintenance of safe levels of selenium exposure in the western San Joaquin Valley.

Table 5. Human Health Effects Associated with Se Exposures.[*]

Dose	Source	Comments
50-200 ug/d	Total Diet	Suggested as "safe and adequate" in the 1980 Recommended Dietary Allowances
100-250 ug/d[**]	Water	No increase in prevalence of 85 abnormal health status indicators
500 ug/d	Total Diet	Estimated consumption in extreme fish-eating Japanese populations; recommended as the tentative maximum permissible intake
590 ug/d	Total Diet	No evidence of toxicity in population from seleniferous region of U.S.
600 ug/d	Diet + Supplement	No evidence of toxic effects in one person after 18 months
2000 ug/d	Supplement	Consumption of $NaSO_3$ for 2 years caused thickened, fragile nails and garlic odor of dermal excretions in one 62 yr old male
3500 ug/d[***]	Supplement	Caused no apparent toxic effects when given to Finnish neuronal ceroid lipofuscinosis patients for 1 year
3200-6690 ug/d	Total Diet	Estimated selenium intake in families in seleniferous region of China
700-14,000[***] ug/d	Total Diet	76% of those interviewed in seleniferous region of U.S. had mild, non-specific symptoms
18,000 ug/d[**]	Water	Consumption for 3 mo. caused hair loss, weakened nails, listlessness in Ute Indian family in Colorado
350,000 ug	Supplement	Single dose induced vomiting, diarrhea, cramps, paresthesias
27,000 ug/d	Supplement	From 1 tablet to 77 tablets over 2½ months caused nausea, nail and hair changes, peripheral neuropathy, garlic breath odor, fatigue, irritability

---

[*] References may be found in Appendix A.
[**] Assumed consumption of 2 liters water/day.
[***] Converted to 70 kg man equivalent.

References

Burau, R.G.; McDonald, A.; Jacobson, A.; May D.; Grattan, S.; Shennan, C.; Swanton, B.; Scherer, D.; Abrams, M.; Epstein, E.; Rendig, V. 1988. Selenium in tissues of crops sampled from the West Side of the San Joaquin Valley, California. In: Selenium contents in animal and human food crops. UC Salinity/Drainage Task Force, Division of Agriculture and Natural Resources, Special Publication [in press].

Pennington, J.A.T.; Church, H.N. 1985. Food values of portions commonly used. 14th ed. New York: Harper & Row. 257p.

Watt, B.K.; Merrill, A.L. 1975. Composition of foods. Agricultural Handbook No. 8. Consumer and Food Economic Institute, Agricultural Research Center, U.S. Dept. Agr. 189p.

CHAPTER 5

Public Health Review of Data and Data Gaps for Boron in the Western San Joaquin Valley

Boron is ubiquitous in the environment, occurring widely in soils, plants, and animals. Boron is found in particularly high concentrations in some regions of the western United States; ground and surface water boron concentrations in the western San Joaquin Valley, for example, have been found as high as 70 and 83 ppm, respectively (Hansen and Morehardt, 1987). This compares to average drinking water concentrations of 0.114 ppm (see Appendix B). Boron is known to be transported through the environment in drainage waters and has been found to occur in exceedingly high levels (reported up to 3390 ppm dry weight; Schuler, 1987) in some plants or seeds where drainage waters have been collected (e.g., Kesterson Reservoir and some evaporation ponds).

Environmental boron has been considered a plant toxicant in the past; however, recent experimental data (*Smith, personal communication) indicate that high dietary boron levels can also cause death and reproductive failures in ducks. The significance of this information for humans is unknown, although severe toxicity of this type in wildlife justifies evaluation as a potential human health concern.

Potential human exposure sources for boron in the western San Joaquin Valley are depicted in Figure 2 (chapter 3). Exposure to these sources may occur by different routes; these have been evaluated for the likelihood that they may contribute to the intake of boron compounds in humans. The primary routes of exposure in humans are: consumption of wildlife, fish, plants (including agricultural crops), livestock and livestock products, ground water and surface water, as well as inhalation and dermal absorption of minerals from air, soil, or water.

Importance of Different Boron Exposure Routes for Human Populations

Only a few sources of data were available to assess the likelihood of exposure to boron from different exposure routes. These are described in chapter 3. Limited data available from the Biological Residue Data Base were used to predict boron ingestion from the consumption of some fish and wildlife in the western San Joaquin Valley (table 6). These values were converted to fresh weight and typical portion sizes as described in chapter 3. Additionally, concentrations of boron in experimentally-induced boron intoxicated wildlife were obtained from some U.S. Fish and Wildlife Service studies (e.g., Smith, personal communication). These values are relevant to boron exposures that may be expected from consumption of locally contaminated wildlife and provide a degree of dose-response information for boron toxicity in animals that otherwise is not available from the scientific literature. Boron concentrations in area crops or domestic animals were not available.

---

*Greg Smith, Ph.D. is a Research Wildlife Biologist with the U.S. Fish and Wildlife Service, Patuxent Wildlife Research Center, Laurel MD.

Table 6. Examples of Boron Concentrations in and Human Exposures from Consumption of Fish in the Western San Joaquin Valley[a]

Source	Tissue	Geographic Area[b]	B Concentration (ppm)[c]		B Exposure (ug/serving)[d]	
			Range of means	Maximum	Typical range	"Worst"
Bluegill	Whole	HC,MS,SJR,MR, SS,VWA	<0.83-1.86	3.89	<83-186	389
Common carp	Whole	PC,GLC,DC,MS,AC CD,HC,LB,SJR,SS	0.68-5.67	6.20	68-567	620
Yellow bullhead	Whole	PC,GLC	<4.3	<4.3	<430	<430
Bent clam	Muscle	MS	9.3	9.3	930	930
Freshwater clam	Muscle	SFC,HC,CD,MS, SS,VWA	2.7-6.3	6.3	270-630	630

---

[a] Data were obtained from the Biological Data Residue Base.

[b] AC, Agatha Canal; CD, Camp 13 Ditch; DC, Deer Creek; GLC, Goose Lake Canal; HC, Helm Canal; LB, Los Banos Creek; MR, Merced River; MS, Mud Slough; PC, Poso Creek; SFC, Sante Fe Grade Canal; SJR, San Joaquin River; SS, Salt Slough; VWA, Volta Wildlife Area.

[c] Concentrations are based on fresh weights; fresh weight conversion factors were obtained from either the respective studies or Pennington and Church, 1985.

[d] Exposures are based on intake (ug) per serving; typical serving sizes are listed in Table 3.

Information from the scientific literature also has been used to assess the relative availability of boron from different exposure routes. This information is more fully described in Appendix B.

Based on the information above, exposure routes have been ranked for their potential contribution to boron exposure in humans in the western San Joaquin Valley. These routes are discussed in the following paragraphs and summarized in table 7. It is important to note, that assignment of ranking to a particular exposure source does not necessarily imply a concomitant health risk associated with that exposure (i.e., a ranking of 3 for an exposure source does not imply a 3-fold greater health risk from this source than from another source with a rank of 1).

Studies have shown that increased boron ingestion in animals leads to higher boron tissue concentrations (Nielsen, 1986; Smith, personal communication). Thus, human consumption of fish and wildlife subjected to high environmental boron would yield greater human exposure to this element than otherwise would be expected from these sources. However, limited monitoring of boron tissue levels in fish and wildlife in the drainage study area and experimental studies of boron-intoxicated ducks have indicated that animal tissue boron concentrations are generally far less than average boron concentrations found in typical plants throughout the United States.

Studies of boron concentrations in plant tissue in the western San Joaquin Valley have been reported only in plants consumed as food by wildlife. Boron concentrations found in some Kesterson Reservoir flora (Schuler, 1987) exceed adverse effect levels for ducks (Smith, personal communication); however, these plants are not known to be consumed by humans. Levels of boron in agricultural produce grown in the drainage area have not been investigated. Similarly, boron concentrations in domestic livestock have not been studied in the western San Joaquin Valley.

The median values for boron found in ground and surface water in the drainage area in 1986 were 6,000 and 1,700 ppb, respectively (Hansen and Morehardt, 1987). Domestic wells near Kesterson Reservoir have been found to contain 7,000 ppb boron (USBR Water-Quality Analyses, see chapter 3). Water is considered a significant source of boron for humans in many areas of the western San Joaquin Valley.

Unlike selenium, boron is not known to be volatilized in the environment. Thus, exposure via inhalation would be limited to breathing dusts containing particulate boron compounds. It is unlikely that exposure to airborne boron would be significant in any environmental setting.

Boron in the form of boric acid is not well absorbed through intact skin. Dermal contact is considered an unlikely source of boron exposure for residents of the western San Joaquin Valley. Hand-to-mouth contact of soil containing high levels of boron is a possible exposure route in small children. Results of a UC - Davis leaching study conducted in 1969 showed that surface soil boron concentrations in the Lost Hills region of the western San Joaquin Valley (a high-boron area) have ranged from 1-14 ppm (reported in Steele, 1983). Even daily consumption of several grams of this soil would not provide a significant source of dietary boron for children.

Table 7. Potential Relative Contribution of Different Routes of Increased Boron Exposure in the Western San Joaquin Valley.

Route	Rank	Comments
WC	U	Wildlife exposed to high environmental boron should have higher tissue boron concentrations than normally expected; however, animal tissue is not a major source of boron for humans.
FC	2	Consumption of fish found in the study area would likely contribute more to boron intake in humans than fish found in other geologic areas; however, boron concentrations found in local fish are still far less than average boron levels found in typical plants foodstuffs.
PC	U	Boron concentrations in agricultural produce in the western San Joaquin Valley have not been reported. It is probable that plant consumption would provide the greatest source of boron in the human diet; however, the relative concentration of boron in agricultural produce from the western San Joaquin Valley compared to produce from other geographic regions is unknown.
APC	U	Boron concentrations in domestic animal products in the western San Joaquin Valley have not been analyzed.
GWC	3	Ground waters have been found to contain higher levels of boron in the drainage area than many other areas of the U.S. Ground water is likely to serve as a major contributor to boron intake in humans.
SWC	3	Many surface water sources also contain relatively high boron levels in the western San Joaquin Valley. If these waters are consumed directly, they would provide a significant portion of the daily boron intake in humans.
BDV	UL	Boron is not known to be volatilized in the environment. Breathing particulate boron dusts would not likely contribute measurably to human boron exposure.
DC	UL	Dermal absorption of boron through intact skin is probably very low. Although direct contact with concentrated boron compounds on abraded skin has caused systemic illness, it is unlikely that this would be an environmentally significant route of human exposure.

WC = wildlife consumption
FC = fish consumption
PC= plant consumption
APC = animal and animal product consumption
GWC = ground water consumption
SWC = surface water consumption
BDV = breathing dusts and volatilzed compounds
DC = dermal contact

U = unknown
1 = least exposure potential
5 = greatest exposure potential

Human Health Effects of Exposure to Boron

Health correlates of exposure to boron compounds are presented in table 8. These examples are referenced and described in more detail in Appendix B. There is a paucity of information regarding human toxicity following boron exposure, especially from environmental sources. From animal studies it appears that male reproductive effects, including testicular degeneration and decreased spermatogenesis, are among the most sensitive known indicators of boron toxicity. There only has been one preliminary study (conducted in Russia) that has addressed this possibility in humans. A tendency toward reduced sexual function in Russian men consuming water with a boron concentration of 0.3 ppm was noted in a small epidemiologic survey [see Appendix B]. This is the only known report of apparent ill-effect from an environmental source of boron. Because other confounding factors that might have affected sexual function were not considered or eliminated, this work should be considered preliminary.

Because of the dearth of information regarding concentrations, forms, and relative toxicities of dietary boron compounds, it is not possible to assess the potential risk from exposure to boron in levels found in the western San Joaquin Valley. Additionally, there is uncertainty surrounding possible physiologic roles for boron in humans and animals.

References

Hansen, S.; Morehardt, J.E. 1987. Identification of potential substances of concern in agricultural drainage waters from the San Joaquin Valley: A screening level analysis. U.S. Bureau of Reclamation Contract No. 5-CS-20-03290.

Pennington, J.A.T.; Church, H.N. 1985. Food values of portions commonly used. 14th ed. New York: Harper & Row. 257p.

Nielsen, F.H. Other Elements: Sb, Ba, B, Br, Cs, Ge, Rb, Ag, Sr, Sn, Ti, Zr, Be, Bi, Ga, Au, In, Nb, Sc, Te, Tl. In: Mertz, W., ed. Trace elements in human and animal nutrition. Vol. 2. New York: Academic Press. p.415-463.

Schuler, C.A. 1987. Impacts of agricultural drainwater and contaminants on wetlands at Kesterson Reservoir, California. Master of Science Thesis, Oregon State University.

Steele, J. 1983. Salt management project in Lost Hills Water District, Kern County, CA. July, 1983.

Table 8. Human Health Effects Associated with Boron Exposures.[*]

Dose	Source	Comments
Unknown	Mouthwash	Consumption of large quantities of mouthwash with boric acid caused total alopecia in 1 person
Unknown	Borax Washing Powder	Daily contact for 6 yrs caused total alopecia in 1 person
600 ug/d[**]	Drinking Water	Tendency toward decreased sexual function in males
1500-2000 mg	Intravenous borax	Caused nausea, vomiting, urgent defecation and micturition, within 2 minutes in 10 patients
2240-3500 mg[***]	Intravenous borax	Caused abnormalities in electrocardiograms in 7 patients
44,800 mg[***]	Oral boric acid	Lowest oral lethal dose reported in humans
602,000 mg[***]	Dermal boric acid	Lowest dermal lethal dose reported

---

[*] References may be found in Appendix B.
[**] Assumed consumption of 2 liters water/day.
[***] Converted to 70 kg man equivalent.

CHAPTER 6

Public Health Review of Data and Data Gaps for Molybdenum in the Western San Joaquin Valley

Molybdenum is found widely in the environment, always in conjunction with other elements. The largest deposits of molybdenum are found in the Western Hemisphere; some regions of the western United States are a particularly rich source. Molybdenum is a required nutrient for microorganisms, plants, and animals. Dietary molybdenum deficiency has never been described in human populations; molybdenum toxicity from natural sources of this element is considered a greater risk to humans than deficiency (NRC, 1980).

Various human exposure sources for minerals, including molybdenum, in the western San Joaquin Valley are depicted in Figure 2 (chapter 3). The primary routes of exposure are: consumption of wildlife, fish, plants (including agricultural crops), livestock and livestock products, ground water and surface water, as well as inhalation and dermal absorption of minerals from air, soil, or water.

Importance of Different Molybdenum Exposure Routes for Human Population

Very few data are available for estimation of human molybdenum exposures in the western San Joaquin Valley. Data from the Biological Residue Data Base and the U.S. Geological Survey (USGS) (see chapter 3) were used to provide molybdenum concentrations in some fish in Kern and Merced Counties (table 9) and water in the Tulare Basin region. As described in chapter 3, fish were converted to fresh weights and typical portion sizes so that human exposures to molybdenum could be estimated.

Information from the scientific literature was also used to assess the importance of some routes of molybdenum exposure (e.g., dermal and inhalation exposures).

Based on the above information, exposure routes have been ranked for their presumed contribution to overall molybdenum intake in human populations in the western San Joaquin Valley. These routes are discussed in the following paragraphs and summarized in table 10. Rankings do not necessarily imply concomitant health risk (i.e., a ranking of 3 for an exposure routes does not mean a 3-fold increase in health risk from this route than from a route with a rank of 1).

Only two species of fish with a few samples each have been analyzed for molybdenum concentrations in the Grasslands area. Concentrations in these fish are quite low compared to overall human molybdenum intake levels and thus would not make a significant contribution to dietary molybdenum; however, the sample size is insufficient to assure that these values are representative of fish throughout the western valley. Data for molybdenum concentrations in area wildlife are not available.

Molybdenum analyses of agricultural crops and domestic animals in the western San Joaquin Valley have not been performed.

Ground and surface waters in the Kesterson area have not been found to exceed those reported for treated water in large U.S. cities. Along the

Table 9. Examples of Molybdenum Concentrations in and Human Exposures from Consumption of Fish in the Western San Joaquin Valley[a]

			Mo Concentration (ppm)[c]		Mo Exposure (ug/serving)[d]	
Source	Tissue	Geographic Area[b]	Range of Means	Maximum	Typical range	"Worst"
Bluegill	Whole	SJR,SS,MR	0.196-0.573	0.68	19.6-57.3	68
Common carp	Whole	PC,GLC,DC SJR,SS,MR	0.099-0.463	1.08	9.9-46.3	108
Yellow bullhead	Whole	PC,GLC	0.086	0.086	8.6	8.6

[a] Data were obtained from the Biological Residue Data Base.

[b] DC, Deer Creek; GLC, Goose Lake Canal; MR, Merced River; PC, Poso Creek; SJR, San Joaquin River; SS, Salt Slough.

[c] Concentrations are based on fresh weights; fresh weight conversion factors were obtained from either the respective studies or Pennington and Church, 1985.

[d] Exposures are based on intake (ug) per serving; typical serving sizes are listed in Table 3.

Table 10. Potential Relative Contribution of Different Routes of Increased Mo Exposure in the Western San Joaquin Valley.

Route	Rank	Comments
WC	U	Measurement of the Mo concentration in wildlife tissue has been very limited. Experimental evidence indicates that animal tissue Mo will increase as a result of greater Mo exposures; however, whether this would provide a signficant source of dietary Mo in humans is unknown.
FC	U	In the few studies reporting fish Mo concentrations in the western San Joaquin Valley, values have been low. However, data are not sufficient to quantify the extent of this exposure source in humans.
PC	U	Data regarding food crop levels of molybdenum in the western San Joaquin Valley have not been reported. A few reports from outside the U.S. have documented negative health effect apparently resulting from high-Mo levels in local foods, but comparison values do not exist.
APC	U	Animal products have not been evaluated for molybdenum content in the drainage area.
GWC	1	Because molybdenum is not a regulated trace element, concentrations of Mo in public drinking water supplies are not measured. Mo concentrations in Kesterson area domestic wells would not contribute significantly to typical levels of intake.
SWC	1	With the exception of the San Luis Drain, surface water Mo concentrations in the drainage area do not appear to be excessive.
BDV	UL	Mo is not known to be volatilized in the environment. Breathing particulate Mo dusts would not likely contribute measurably to human Mo ingestion.
DC	UL	Dermal absorption of Mo compounds via the skin has not been reported and, consequently, is probably very low.

WC = wildlife consumption
FC = fish consumption
PC = plant consumption
APC = animal and animal product consumption
GWC = ground water consumption
SWC = surface water consumption
BDV = breathing dusts and volatilized compounds
DC = dermal contact

U = unknown
UL= unlikely
1 = least exposure potential
5 = greatest exposure potential

western side of the Tulare Basin, however, domestic well waters have been found to contain up to 160 ppb molybdenum (see chapter 3). Although a federal drinking water standard for molybdenum has not been set, this concentration of molybdenum in drinking water would provide 64% of the maximum recommended "safe and adequate" level of intake for this element (see below).

Although data do not exist regarding absorption rates of inhaled molybdenum compounds in humans, inhalation is considered an unlikely route of molybdenum exposure in humans in the western San Joaquin Valley. Evidence has not been found in the scientific literature to indicate that inhalation exposures to molybdenum in environmental settings have caused harm in humans.

Similarly, data on skin absorption of environmental molybdenum sources have not been reported. There is no indication that dermal contact is a major route of molybdenum exposure for residents of the drainage area. Hand-to-mouth ingestion of high-molybdenum soils would be a possible route of human molybdenum exposure, particularly in small children. Although molybdenum concentrations in valley soils have not been well mapped, this is considered an unlikely route of significant molybdenum exposure.

Human Health Effects of Exposure to Molybdenum

Health correlates of exposure to molybdenum compounds are presented in table 11. These examples are referenced and described in more detail in Appendix C. The 1980 Recommended Dietary Allowance estimated that 150 to 500 ug/day is a "safe and adequate" level of molybdenum ingestion for adults in the U.S. population. Dietary levels of molybdenum only slightly higher (540 ug/day) have been reported to cause increased copper excretion in humans. Thus, only marginally high dietary levels of molybdenum may have a negative impact on copper status in humans. Insufficient information regarding the concentration of molybdenum in local food and water supplies severely restricts assessment of molybdenum consumption levels in western San Joaquin Valley residents. Levels of molybdenum intake in the United States have been estimated to range from 120-240 ug/day (see Appendix C). These levels may be exceeded by consumption of water alone in some areas of the Tulare Basin; however, the public health significance of this cannot be determined without information regarding the total dietary exposure to molybdenum in the region.

References

National Research Council (NRC), Food and Nutrition Board. 1980. Recommended Dietary Allowances. 9th Rev. Washington, D.C.: National Academy Press. 185p.

Pennington, J.A.T.; Church, H.N. 1985. Food values of portions commonly used. 14th ed. New York: Harper & Row. 257p.

Table 11. Human Health Effects Associated with Mo Exposures.*

Dose	Source	Comments
150-500 ug/d	Total Diet	suggested as "safe and adequate" in the 1980 Recommended Dietary Allowances
540 ug/d	Total Diet	consumption of high-Mo sorghum increased copper excretion nearly 3-fold compared to a low-Mo diet
Unknown	Total Diet	consumption of high-Mo sorghum may have exacerbated development of osteoporosis in a region of India
10,000- 15,000 g/d	Total Diet	a medical survey in a high-Mo 15,000 ug/d region of Russia indicated increased revalence of a gout-like disorder

*References may be found in Appendix C.

APPENDIX A

SELENIUM

I. INTRODUCTION

Selenium (Se) has long been recognized for its toxic properties; Se was the first element identified in native vegetation in levels sufficient to cause intoxication in animals (Allaway, 1968). Se first came to environmental and political prominence in California in 1983, when researchers at the U.S. Fish and Wildlife Service (USFWS) observed unusual numbers of dead and deformed aquatic birds at Kesterson Reservoir in the western San Joaquin Valley (Letey et al., 1986). Kesterson Reservoir consists of a series of 12 interconnected holding ponds that serve as the terminus of the San Luis Drain, a man-made canal designed to remove subsurface drainage waters from western San Joaquin Valley agricultural lands. Some of this land was later determined to contain naturally elevated Se levels; localized leaching of Se into drainage waters apparently occurred. Subsequent testing of water, waterfowl, fish, and local flora in the Kesterson area supported the conclusion that Se intoxication was at least partly the cause of observed avian abnormalities (Letey et al., 1986; Presser and Barnes, 1984; 1985). Within the year, ponds located in the reservoir were closed to the public and the California Department of Health Services had issued a health advisory recommending limited consumption of waterfowl from the Kesterson area (Letey et al., 1986). Plans were later completed to cease flow of drainage waters into the San Luis Drain.

Se is a difficult element to regulate because of its narrow margin of safety (NRC, 1977); i.e., the difference between the effective dose (as a required nutrient) and the toxic dose is small [approximately 10- to 20-fold in most animal species (Combs and Combs, 1986h)]. Because of Se's relatively high toxicity and its ability to be accumulated in the biological environment, Se has been identified as a substance-of-concern in agricultural drainage waters of the western San Joaquin Valley (SWRCB, 1987). Attempts to assess and regulate environmental Se as well as to predict human health consequences of excessive exposure to this element are ongoing. Studies to evaluate the potential impact of Se and other drainage contaminants in California currently are being conducted by state and federal agencies and the University of California.*

II. OCCURRENCE

A. Natural

Se is extensively distributed in the earth's crust with an average concentration estimated at 0.09 ppm (Venugopal and Luckey, 1978). Igneous rocks, hydrothermal deposits, and sulfide and porphyry copper deposits provide the greatest abundance of Se (NRC, 1983b); however, the most significant agronomic source of Se is sedimentary rock, the parent material of many soils (Combs and Combs, 1986b). Although most soils contain between 0.1 to 2 ppm Se (NRC, 1983b), certain seleniferous regions in the United States and elsewhere may contain much higher Se concentrations.

---

*Some portions of the following report were prepared for and presented at the UC Salinity/Drainage Task Force conference, March 6-7, 1987, Sacramento, CA.

B. Anthropogenic

Se also occurs in certain environments as a result of industrial or agricultural processes. Coal or crude oil may contain relatively high Se in some areas and may be redistributed to the environment during combustion (Shamberger, 1983b). Se compounds are used commercially in the manufacture of glass and ceramics, rubber, rectifiers, photoelectric cells, semiconductors, veterinary pharmaceuticals, antidandruff shampoos, and as pigments in the ink and paint industry (Berman, 1980; Carson, 1986; NRC, 1983b; Shamberger, 1983c; Wilber, 1980). Additionally, Se may be added to the environment as a constituent of sewage sludge; levels in raw sewage may reach 1 to 5 ppm (Baird et al., 1972; NRC, 1977; USEPA, 1982). As mentioned previously, irrigation of seleniferous lands for agricultural purposes, with subsequent translocation of high-Se drainage waters, has caused a significant increase in environmental Se in Kesterson Reservoir. Mean Se concentrations in the top 6 inches of sediment in refuge ponds have ranged from 2-35 ppm (reported in Fan et al., 1988). Sediments found in the San Luis Drain have ranged from 3-210 ppm Se (dry weight) (reported in Fan et al., 1988).

Individuals may also come in contact with excessive Se through ingestion of Se-containing vitamin and mineral supplements, although this would only be as a result of errors in use and/or formulation. Only a few cases of intoxication via this route are known to have occurred (see section VI.B). Untoward health effects resulting from chronic low level supplementation have not been recognized.

III. ENVIRONMENTAL FATE

A. Chemical forms

Selenium is similar, in some ways, to the physical and chemical characteristics of sulfur and tellurium, having properties of both metals and nonmetals (Combs and Combs, 1986a; Hogberg and Alexander, 1986; Venugopal and Luckey, 1978). Se occurs naturally in four oxidation states: -2, selenides; 0, elemental Se; +4, selenites; and, +6, selenates (NRC, 1977), and is capable of forming numerous types of compounds, including oxides and oxyacids, halides, oxyhalides, polyatomic cations, organic compounds, and a nitride (Wilber, 1980). Se is typically found in soils as elemental Se, basic ferric selenite ($Fe_2(OH)SeO_3$), calcium selenate, and organic Se analogues of sulfur amino acids (selenides) (Buell, 1983). In water, Se is usually found as selenite or selenate; in western San Joaquin Valley water, selenate is believed to be the predominant form.

B. Availability of Selenium

The major determinant of environmental Se availability is the chemical form in which the element exists in soils and sediments. Chemical forms and concentrations of Se in soils are believed to be related to oxidation-reduction potential, pH, and the solubility of Se complexes with other constituents (Allaway, 1968; Cary et al., 1967; Geering et al., 1968; Gissel-Nielsen, 1971; NRC, 1983b). Factors contributing to excessive accumulation of environmental Se in vegetation have been summarized by the National Research Council (NRC, 1971; 1983b); accumulation may occur under two sets of circumstances:

- In areas of low (< 8 cm) annual rainfall, where rocks with a high content of Se decompose to form well-drained soils, insoluble forms of selenium will be converted to selenates and organic Se compounds which are available to plant material. These soils may produce vegetation containing potentially toxic levels of Se.

- In areas of alkaline soils (such as those in the western San Joaquin Valley), where rocks with a high content of Se decompose to form poorly-drained soils or where Se from one area may be deposited in an area of poorly-drained soil by alluvial action, vegetation containing potentially toxic levels of Se may be produced. This problem may be exacerbated if aeration of these soils is improved by artificial drainage.

Selenates are considerably more soluble than corresponding selenite compounds (NRC, 1983a) and are thus better absorbed from water or soil by plants (NRC, 1977). In alkaline and oxidizing environments, the solubility and stability of selenates are greatest and conversion to less stable selenite and elemental Se is quite slow (NRC, 1983a). Under acidic and reducing conditions, formation of insoluble elemental Se or a ferric iron-selenite complex is promoted, greatly decreasing availability (Demayo et al., 1979; NRC, 1983a,b). Although considered largely unavailable, there is evidence that significant amounts of elemental Se may be oxidized in neutral and alkaline soils to more soluble forms (i.e., selenites and selenates) (Geering et al., 1968). Additionally, some organic Se compounds present in soils may also be available for plant uptake (NRC, 1983b).

Once an available source of Se is present in the soil, actual uptake of Se by the plant depends largely on plant species; these are divided into 3 categories: (1) primary indicators, which include many species of _Astragalus_, _Machaeranthera_, _Haplopappus_, and _Stanleya_, and may accumulate Se to levels of several thousand ppm (dry matter basis); (2) secondary Se accumulators, including plants from the genera _Aster_, _Striplex_, _Castelleja_, _Grindelia_, _Gutierrezia_, _Machaeranthera_, and _Mentzelia_, the tissues of which rarely exceed more than a few hundred ppm Se, and, (3) non-accumulators, including the common food/feed grains, grasses, and many weeds, the tissues of which rarely exceed a few ppm Se (NRC, 1983b; Rosenfeld and Beath, 1964a).

Chemical forms and levels of Se found in human and animal crops have not been well characterized. Early studies in seleniferous regions of the western U.S. indicated that wheat, corn, rye, onions, barley, oats, and asparagus contained a maximum Se concentration between 10-30 ppm (dry weight) (Rosenfeld and Beath, 1964a). Rutabagas, cabbage, peas, beans, carrots, tomatoes, and beets contained significant, but lesser amounts of Se. Peas and barley grown on seleniferous soils in Colombia, South America were found to contain over 135 ppm Se (Ancizar-Sordo, 1947).

Combs and Combs (1986c) have compiled fresh weight Se levels of various foods grown in low, moderate, and high Se areas of the world. (Because of the extremely high water content of many foods as consumed, comparison of mineral [or other constituent] content of food items on a fresh weight basis proves less misleading than dry matter basis comparisons for estimating potential exposure.) Even within the United States, food products vary dramatically (several-fold or more) in Se content depending on geographic region. Se content of most foods (fresh weight basis) in high Se areas is generally a few tenths of a ppm (a few hundred ppb's) or less. With the possible exception of wheat and brazil nuts, which, on occasion, have been reported to contain in excess of 20 ppm Se (fresh weight) when grown in seleniferous regions of the U.S., few food items have been shown to contain more than 1 or 2 ppm Se.

Se appears to concentrate in crops as a function of that plant's sulfur requirement. Thus, cruciferae generally contain the most selenium, followed by legumes and then cereals (Rosenfeld and Beath, 1964a). Se content may vary greatly from part to part within each plant; Se in milled wheat, for example, has been found to be highest in the bran portion. This probably relates to different distribution patterns of Se-containing proteins between various tissues. Differential content of Se within a plant may be influenced by the form of Se absorbed (Rosenfeld and Beath, 1964a).

Although soil conditions and plant species tend to play the largest roles in determining Se levels of plant tissues, other factors may also be significant. Climactic conditions that influence crop production (e.g., temperature and humidity) may have a profound affect on Se levels of specific plants in a given area from year to year (Combs and Combs, 1986c). Conditions that favor high yields generally lower mineral content over average or low yield conditions. Variety of plant species, the interaction of variety with soil type, and the stage of plant growth can also cause large variations in the Se contents of crops (Combs and Combs, 1986c; Rosenfeld and Beath, 1964a).

C. Mobility

Bioconcentration refers to the ability of plants and animals to accumulate a compound in their tissues in amounts greater than the concentration of that compound in the surrounding environment or food that they consume (Letey et al., 1986). Algae has been estimated to concentrate Se from water by factors of 100 to 2,600; aquatic organisms have been known to concentrate selenium 32,000-fold in excess of ambient water concentrations (Eisler, 1985; Letey et al, 1986). Whether Se levels are progressively magnified through higher aquatic food chains is not currently known. Accumulation of Se from environmental sources may be altered by a number of factors, including water temperature, age of the organism, tissue and species specificity, mode of administration, and form of selenium (Eisler, 1985).

Similar to several other metals, Se is mobilized in the environment partially through volatilization. Se has been shown to be volatilized, predominantly in the form of dimethylselenide, from soil, lake sediment, plants, and animals (Abu-Erreish et al., 1968; Chau et al., 1976; McConnell and Roth, 1966; Zieve and Peterson, 1981; Zieve and Peterson, 1984). The degree of volatilization is dependent on temperature, moisture, time, water-soluble selenium concentration, microbial activity, and season; volatilization activity for soil has been shown to be highest in the spring (Zieve and Peterson, 1981).

IV. ESSENTIALITY/BIOLOGICAL FUNCTION

Long recognized as a toxic element, it was not until 1957 that the nutritional significance of Se was recognized (Combs and Combs, 1986f). Schwarz and Foltz (1957), Schwarz et al. (1957), and Patterson et al. (1957) noted the ability of dietary Se to prevent liver necrosis in rats and exudative diathesis in chicks. Other mammalian and avian diseases which had been thought simply the result of vitamin E deficiency were later shown to be responsive to Se as well as vitamin E (Burk, 1984; Dutkiewicz et al., 1972; Muth et al., 1958; Nesheim and Scott, 1959). Thompson and Scott (1969) and McCoy and Weswig (1969) established Se as an essential trace mineral independent of dietary vitamin E, which was supported by further studies (Sprinker et al., 1971; Thompson and Scott, 1971).

Se was later discovered to exist as an essential component of glutathione peroxidase (SeGSHpx) (Rotruck et al., 1973). This enzyme serves to protect against cellular damage from free radical chain reactions, apparently by preventing initiation of lipid peroxidation (Combs and Combs, 1986f). SeGSHpx has also been shown to play a role in prostaglandin metabolism, catalyzing the conversion of L-12-hydroperoxy-5,8,11,14-eicosatetraenoic acid (12-HPETE) to the corresponding hydroxy compound 12-HETE (Combs and Combs, 1986f). As HPETE helps to regulate synthesis of prostacyclin, an important antiaggregatory compound, Se deficiency is believed to lead to increased platelet aggregation (Combs and Combs, 1986f). Conversely, excessive Se can cause a predictable dose-response increase in prostacyclin levels, with resulting antiaggregatory activity. This may explain increased bleeding times in volunteers consuming Se as a dietary supplement (Combs and Combs, 1986f; Schiavon et al., 1984).

Se also appears to have other biologic functions, some of which may be independent of glutathione peroxidase. Animal studies have indicated that Se deficiency affects the hepatic xenobiotic-metabolizing system, including biotransformation and conjugation phases (Combs and Combs, 1986f). Because xenobiotic metabolism can serve to either activate or detoxify a compound, depending on its chemical properties, exposure to various foreign compounds may have vastly different effects in the Se deficient animal (Combs and Combs, 1986f). Additionally, Se may be involved in heme metabolism and has been shown to be required for normal spermatogenesis in several mammals and possibly birds (Combs and Combs, 1986f).

An endemic cardiomyopathy, Keshan disease, occurred in post-weaning infants, children, and women of childbearing age in rural Chinese populations where very low levels of Se are encountered. The disease affected as much as 11% of certain populations in these age groups, with a case fatality rate approaching 80%. Although the etiology has not been completely elucidated, Se deficiency is generally considered to contribute to Keshan disease (Chen et al., 1980; Combs and Combs, 1984). Se supplementation has been used successfully as a preventive measure. Kaschin-Beck disease also appears to be a Se-responsive disorder occurring in certain Asian populations (Combs and Combs, 1986g). This disease results in enlarged joints and, occasionally, dwarfism. As is also postulated in the case of Keshan disease, Kaschin-Beck disease is not believed to result solely from Se deficiency; other, possibly environmental, factors are suspected in the etiology of these syndromes (Combs and Combs, 1986g). Various signs and symptoms, particularly peripheral neuropathies, have been reported in patients receiving total parenteral nutrition or consuming restricted diets low in Se; one death is known to have occurred (Johnson et al., 1981; van Rij et al., 1979).

V. TOXICOKINETICS

The metabolic fate of Se has been reviewed by numerous authors (Bopp et al., 1982; Buell, 1983; Combs and Combs, 1984; Combs and Combs, 1986e; Diplock, 1976; Ganther, 1979; Ganther, 1986; Hogberg and Alexander, 1986; Levander, 1976a; Martin and Gerlach, 1972; NRC, 1983c; Shamberger, 1983a; Venogopal and Luckey, 1978).

A. Absorption

Investigations have shown that, when fed to animals, selenite, selenate, selenomethionine, and the Se present in corn or animal tissues are readily and fairly efficiently absorbed, mainly in the duodenum and other parts of the small intestine (Bopp et al., 1982; Buell, 1983; Whanger et al., 1976). Selenite and selenate absorption mimic sulfite and sulfate absorption, respectively. Selenomethionine absorption mimics that of methionine (Fox and Jacobs, 1986). Dietary form of Se appears to affect absorption rates, with Se in protein-bound forms generally absorbed to a greater extent than inorganic salts of the element (NRC, 1983c). Elemental Se and selenium sulfide reportedly are poorly absorbed from the digestive tract (Buell, 1983, Cummins and Kimura, 1971; Hogberg and Alexander, 1986). Absorption of selenite in animals does not appear to be controlled through a regulatory mechanism (Brown et al., 1972), although absorption may be competitively inhibited by other dietary constituents (Combs and Combs, 1986e). Results from human apparent absorption trials are summarized in Combs and Combs (1986d). Se compounds differ widely in absorption rates, but most studies indicate that, in general, 70% or more of most dietary Se is absorbed.

Utilization of dietary constituents is frequently termed "bioavailability". In the case of minerals, this involves "1) the chemical and/or physical availability in a gastrointestinal tract, that is, the proportion of an ingested mineral that is available for absorption; 2) the different steps of absorption including the uptake of a mineral into the mucosal cell, transport across the cell and transfer into the circulation; 3) a transformation of a mineral into its biologically active form" (Mutanen, 1986). The bioavailability of Se (and other trace elements) may be affected by dietary factors (e.g., levels of intake, interactions with other dietary constituents, food processing, and drugs), host factors (e.g., nutritional, physiological and pathological states), and environmental factors (e.g., infectious agents and personal lifestyle habits) (Young et al., 1982). Methods of estimating Se bioavailability have been well reviewed (Combs and Combs, 1986d; Mutanen, 1986; Young et al., 1982). As with apparent absorption trials, results of bioavailability studies vary considerably. In general, however, Se appears to be highly or moderately available from plant sources (particularly wheat and alfalfa) and relatively less availability from animal sources, although exceptions do occur (Combs and Combs, 1986d; Mutanen, 1986; Young et al., 1982). Data on availability of selenium from fish sources are conflicting. In certain cases, Se has been found to be very poorly available from fish or fish products, presumably because of binding to other constituents such as heavy metals; however, other reports have indicated that Se from various fish sources may be highly available under some conditions (Mutanen, 1986).

Data regarding inhalation and dermal absorption of Se are very limited. Following exposure to airborne agents, particles may be deposited in the upper respiratory tract or alveolar region of the lung, transported to the gastrointestinal tract by mucociliary clearance (Medinsky et al., 1981), or absorbed through the skin. Thus, determination of absorption from inhalation exposures must consider all of these routes. Medinsky et al. (1981) conducted an inhalation study with rats using elemental Se and selenious acid, the primary selenium products released from burning of fossil fuels. Less elemental Se and selenious acid were absorbed in the nasal passages than either the gastrointestinal tract or the lungs; however, 58% of elemental Se and greater than 89% of selenious acid initially deposited in the upper respiratory tract were ultimately absorbed into the blood. Although both of these compounds were rapidly and largely absorbed from the lung, elemental Se was absorbed more slowly than selenious acid. Additionally, 9-27% of selenious acid applied to the skin was absorbed over a 9-day period. Dermal absorption of sodium selenite in rats has also been reported (Dutkiewicz et al., 1972). Various industrial accidents indicate that inhalation absorption and resulting toxicity from some Se compounds do occur in humans (Cooper, 1967).

B. Distribution/Detoxification

Once absorbed, the majority of Se is bound to plasma proteins (primarily very low-density lipoproteins) and distributed throughout the body by the circulatory system (Burk, 1974; Combs and Combs, 1984). Studies in different animal species have shown that Se tends to concentrate in detoxifying organs with liver, kidneys, spleen, and lungs containing the greatest amounts. Intestinal tissue may also contain significant concentrations of Se, as does cardiac muscle and hair. Nervous tissue contains relatively little Se and fat is essentially devoid (NRC, 1983c; Shamberger, 1983a). Human tissue studies have revealed that mean highest Se content (on a wet weight basis) is found in kidney (1.09 ppm), followed by liver (0.54), spleen (0.34 ppm), and testis and pancreas (0.30 ppm each). Hair contained 0.57 ppm Se. The lowest Se levels were found in brain (Schroeder et al., 1970).

At the metabolic level, Se in levels sufficient to meet nutritional needs is incorporated into SeGSHpx. When consumed in greater amounts, the excess inorganic selenium will be converted into excretable metabolites. Some organic Se compounds (e.g., selenomethionine), however, may bypass this mechanism and be incorporated into general body proteins as an analog of sulfur (e.g. in place of methionine) (Burk, 1976; Cary et al., 1973; NRC, 1977; Sunde et al., 1981). This may especially be true under conditions of limiting dietary methionine (Fox and Jacobs, 1986). De novo synthesis of these compounds from inorganic Se forms does not occur, thus inorganic Se is not incorporated into body proteins other than GSHpx (Fox and Jacobs, 1986).

The extent of Se accumulation in various tissues depends on tissue type, level of Se ingested, individual physiological variation, and chemical form of Se (Martin and Gerlach, 1972). For the reasons defined above, Se consumed in organic form generally accumulates to a greater extent in the animal tissue than Se consumed in inorganic form (Cary et al., 1973; NRC, 1983c).

In contrast to sulfur, which is generally oxidized in vivo, the primary metabolic fate of Se is reduction (Combs and Combs, 1984; Ganther, 1986). Selenate may be enzymatically activated in vivo with ATP, undergoing subsequent nonenzymatic reduction to selenite via glutathione (Ganther, 1986). Selenite is readily reduced to elemental Se and hydrogen selenide; the latter reaction occurring in liver and erythrocytes, and, perhaps, other tissues (Ganther, 1986). The resulting selenide can undergo methylation in the liver, which appears to be a detoxification pathway (Bopp et al., 1982; Ganther, 1979; Martin and Gerlach, 1972). Metabolism of the selenoamino acids (e.g., Se-methionine, Se-cystine) is believed to resemble that of the sulfur amino acids (e.g., methionine, cystine), undergoing transsulfuration or transamination (Ganther, 1986), with subsequent degradation to selenide (Combs and Combs, 1984). Although these reactions have been demonstrated, the intermediary metabolism of Se is largely unknown. These reactions may not be relevant at all levels of Se status.

C. Excretion

Under conditions of normal levels of intake, Se is excreted predominantly in the urine, mainly as the metabolite trimethylselenonium [$(CH_3)_3Se^+$]. This mode of excretion occurs regardless of Se form ingested (Ganther, 1986). Notable levels of Se may also be excreted in feces and sweat (Snyder et el., 1975). At levels of intake above physiologic requirements, the third methylation step appears to become rate-limiting, and dimethylselenide, excreted via the pulmonary system (McConnell and Roth, 1966), becomes a more significant metabolite (Ganther, 1986).

Although absorption is not affected by the previous Se status of the individual, the length of time that a given dose of Se is retained in the body is greatly dependent on the previous Se status (NRC, 1983c) as well as chemical form of Se (Bopp et al., 1982; Griffiths et al., 1976; Lathrop, et al., 1972; Thomson, 1974). Robinson et al. (1985) compared renal Se clearance rates of New Zealanders (average daily selenium intake <30 ug) to those of U.S. subjects (average daily selenium intake approximately 80 ug) (Levander et al., 1981). Results suggest that New Zealanders may have adapted to low Se intakes by excreting an unusually low proportion of Se circulating through the kidneys. U.S. subjects, in contrast, did not reduce plasma Se clearance rates when fed Se-depleting diets. Further evidence that the kidney plays the primary homeostatic role in Se nutriture was advanced in a study of 4 U.S. male adults given single or multiple oral doses of a stable Se isotope ($^{74}SeO_3$) (Janghorbani et al., 1982). Increasing dosage levels resulted in a smaller proportion of the absorbed Se being retained. Interestingly, newly absorbed Se was preferentially excreted over Se previously equilibrated in the plasma pool. This may have important implications for the use of urinary Se as a measure of Se intake or status (see section IX) (Janghorbani et al., 1982).

Pulmonary excretion of Se is also affected by previous exposure to the element (Magos et al., 1987). Isotopic studies showed that rats pretreated with Se had lower liver selenium levels and increased dimethylselenide excretion following injection of sodium selenite. The authors speculated that dimethylselenide excretion after a challenge dose might prove useful as a diagnostic screening test for identification of high exposure groups. This method has not been validated or standardized, nor is it currently practiced.

In humans, Se excretion is triphasic, with half-lives of the terminal elimination phase reported to average 4 months and 7-8 months for selenite and selenomethionine, respectively (Bopp et al., 1982; Griffiths et al., 1976; Lathrop et al., 1972; Thomson and Stewart, 1974). Excretion rates of Se generally peak in the first two hours following a supplemental dose (Thomson, 1974); however, overall excretion is relatively slow. Only 11% of a 54 ug dose of ^{74}Se was excreted in the first 24 hours (Janghorbani et al., 1982); this value was similar to those obtained in other studies (Jereb et al., 1975; Thomson, 1974).

Intake of several substances can alter elimination of Se. Inorganic mercury and thallium have been shown to decrease pulmonary excretion of methylated Se compounds (Levander and Argrett, 1969). Similarly, arsenic may inhibit production of excretable methylated Se compounds; however, it has also been shown to increase the toxicities of those same compounds (Hogberg and Alexander, 1986; Levander and Baumann, 1966a,b; Levander and Argrett, 1969; Obermeyer et al., 1971). Arsenic can modify Se metabolism by increasing biliary and fecal excretion of Se several fold (Levander and Argrett, 1969; Levander and Baumann, 1966a,b).

When forms of Se subject to homeostasis are consumed in amounts greater than the capacity of the excretory system, accumulation in the human or animal body will begin (Burk, 1976) and toxicity may result.

VI. TOXICITY

A. Animal

1. Acute/Short-term Exposures

A disorder believed to have been Se toxicity resulting from plant ingestion in horses was noted as early as 1295, during the travels of Marco Polo [reported in Buell, 1983]. Polo recorded such symptoms as painful feet and loss of hooves when animals consumed a particular plant that grew near Tibet. Similarly, in 1860, an army surgeon noted tenderness and inflammation of the feet and loss of hair from the mane and tail of horses grazing near Fort Randall (South Dakota). Symptoms were noted approximately 10 days after animals were moved to the area and ceased after other forage was provided [reported in Buell, 1983]. By the 1930's, toxic effects of these feedstuffs had been documented in the laboratory and Se had been identified as a potentially toxic constituent (Franke, 1934a). Subsequently, the condition of "blind staggers" was identified as the acute disorder occurring as a consequence of consumption of high levels (up to several thousand ppm) (Buell,

1983) of non-protein selenoamino acids present in some "accumulator" plants (Trelease, 1960; Shrift and Virupaksha, 1965). Blind staggers is often fatal, following the development of blindness and staggering (Olson, 1986). Recent evidence, however, has led some researchers to believe that non-Se compounds found in accumulator plants may be at least partially responsible for development of this syndrome (Buell, 1983).

Combs and Combs (1986h) have reviewed studies of acute and subacute Se toxicity in laboratory animals. Signs resulting from single or a few doses of excessive Se include lassitude, garlic breath odor, vomiting, shortness of breath, muscle tremors, neurological impairments, and respiratory failure. Hepatic and renal damage, endocarditis, myocarditis, smooth muscle degeneration of intestinal organs, and long bone erosion were found upon pathological examination (Combs and Combs, 1986h). The dose(s) of Se that have been required to elicit such effects have varied with chemical form, mode of administration, and animal species. Sodium selenite, sodium selenate, selenomethionine, and selenocystine (the latter two believed to be the predominant forms of Se in common foodstuffs) appear to have similar acute toxicities, with oral LD_{50} values as low as 1.8 mg/kg body weight (sodium selenite in rabbits) (Combs and Combs, 1986h). Reduced growth rate in immature animals is usually the first sign of Se toxicity; 2.6 ppm Se fed to rats for 4 weeks (in the form of high-Se wheat and oats) caused a 10% reduction in growth rate. Similar results have been found with 3 ppm Na_2SeO_3 provided in the drinking water of rats for 63 days. Growth rate was also reduced (8%) in mice provided 1.8 ppm Se (as Na_2SeO_3) in drinking water for 48 days. Other studies have not shown a deleterious effect following exposure to Se at these levels.

In addition to route of administration, many other factors may affect acute Se toxicity. One such factor may be age; significantly less mortality occurred following a single injected dose of selenite to 10-day-old rats than to 2-month-old rats (Ostadalova et al., 1978). However, a cataractogenic effect, either permanent or intermittent, appeared as a result of selenite toxicity only in early postnatal development (up to the age of 15 days) (Ostadalova et al., 1979). Other authors have confirmed the cataractogenic effect of injected selenite in rat pups (Bunce and Hess, 1981).

Delayed toxicity following short-term Se exposure may occur. Rats developed ascites and edema 2 months after receiving 0.15 mg Se/day for 3 weeks (Rosenfeld and Beath, 1964b).

2. Chronic Exposures

Selenosis in animals resulting from long-term ingestion of relatively low levels (up to 35 ppm) of Se present in plants as protein selenoamino acids (Franke, 1934b; Painter and Franke, 1936; Peterson and Butler, 1962) is called alkali disease (Buell, 1983). Signs include loss of long hair, inflammation of the coronary band (at the base of the hoof), atrophy of the heart, kidney damage and reproductive failure (Olson, 1986). Chronic toxicity studies of Se compounds in laboratory and farm animals have been reviewed and tabulated by Combs and Combs (1986h); results vary depending on factors discussed in the previous section. Eight ppm Na_2SeO_3 provided in drinking water for 47 weeks reduced growth rates by 44% in mice; however, survival of these animals was increased compared to controls. When fed as high-Se corn, 7.2 ppm dietary Se reduced gain and caused anorexia in dogs over a period of 189 days. Growth rate was also reduced (8%) in mice provided 1.8 ppm Se (as Na_2SeO_3) in drinking water for 48 days. Studies have not been designed to compare relative toxicities of different selenium compounds administered on a chronic basis (Combs and Combs, 1986h).

B. Human

1. Acute/Short-term Exposures

Although the 1980 Recommended Dietary Allowances indicated that disease states attributable to dietary Se deficiency or excess had not yet been described in human subjects (NRC, 1980), a number of isolated cases of human toxicosis have been reported over the years. Additionally, acute, sometimes fatal, Se toxicity has been reported rarely as a consequence of self-medication (Sioris et al., 1980; Snodgrass et al., 1981), or accidental (Carter, 1966), suicidal (Civil and McDonald, 1978; Koppel et al., 1986; Matoba et al., 1986; Pentel et al., 1985), and occupational exposures (Ducloux et al., 1977; Schellman et al., 1986).

At least one case of acute Se intoxication from a natural source has been noted in the literature. A case report from Caracas, Venezuela described a 54-year-old man who suffered anxiety, chills, diarrhea, fever, anorexia, and weakness after consuming 70 to 80 "Coco de Mono" (*Lecythis ollaria*) almonds while on a hunting trip (Kerdel-Vegas, 1964). Eight days after consuming the nuts, the subject suffered extensive loss of scalp and body hair. Approximately 1 week later he developed a violet streak over the proximal part of his nails which disappeared within 3 days. Although the authors did not determine the pharmacologically active agent in *Lecythis ollaria*, subsequent reports have identified the factor as seleno-cystathionine (Aronow and Kerdel-Vegas, 1965; Kerdel-Vegas et al., 1965). This compound is also found in *Astragalus pectinatus* and *Stanleya pinnata* (Kerdel-Vegas et al., 1965), two of the selenium accumulator species (Combs and Combs, 1986b).

Other cases of Se toxicosis have also resulted from direct consumption of Se-containing products. Acute Se poisoning was reported in 5 individuals who consumed sodium selenate intended for use as a supplement for turkey diets (Sioris et al., 1980). Symptoms included nausea, vomiting, diarrhea, abdominal pain, chills and tremors. The actual level of Se intake was unknown or unreported; however, mean initial serum Se levels after ingestion were 0.41 to 0.89 ug/ml (normal: 0.2 ug/ml) and mean 24-hour urinary Se excretion was 1175 to 4365 ug (normal: 125 ug). Symptoms resolved within 24 hours of ingestion and all patients were reported well 8 months after the incident.

In 1984, symptoms of acute Se intoxication occurred in 13 individuals who consumed a superpotent over-the-counter Se supplement (FDA Drug Bulletin, 1984; Jensen et al., 1984; Helzlsouer et al., 1985). Analysis of several Se tablets in a lot manufactured for Brite Years, Inc., revealed a Se content 182 times higher than labeled (approximately 30 mg per tablet, in the form of sodium selenite and elemental Se). Estimates of ingested doses of the product ranged from 27 to 2310 mg of Se (from a single tablet to 77 tablets taken over a 2 1/2 month period). Signs and symptoms of toxicity included nausea, abdominal cramps, nail and hair changes (including total alopecia), peripheral neuropathy, garlic breath odor, fatigue, and irritability. Se content of nails was the highest ever reported in the U.S. (8.1 ppm), and red blood cell Se levels were elevated as much as 5 months following exposure. However, in most cases, hematological evaluation as well as liver and renal function tests were normal. Follow-up of subjects indicated that all patients with peripheral neuropathies still have signs such as reduced nerve conduction rates and paresthesias ([**]Jacobs, personal communication). Additionally, of the 3 patients contacted 2 years after consumption of the product, two had developed cataracts and one, never having dental caries previously, had developed severe spontaneous tooth decay (Jacobs, personal communication).

Hogberg and Alexander (1986) report an unpublished account of a 35-year-old woman who consumed 10 grams of a cereal to which 35 mg/g Se had been added. Subsequent analysis indicated that one-third of that supplement was in the form of selenite; the rest was presumed elemental Se. Symptoms included vomiting, diarrhea, cramps, and paresthesias. Although these symptoms were relieved within days, the woman later developed irregular menstrual bleeding and marked hair loss.

2. Chronic Exposures

The ramifications of chronic exposure to low or moderate levels (in excess of requirement) of Se have not been well studied. Possible chronic Se toxicity resulting from long-term industrial exposure has been reported (Diskin et al., 1979), although the patient presented with a myocardial infarction from which he subsequently died. The authors suggested that such chronic exposure may have caused pathologic pulmonary changes (perivascular noncaseating granulomas) found during histological evaluation on autopsy and consistent with development of "rose cold" symptoms of cough, sore throat, and bronchitis described by Hamilton (1925) and Motley et al. (1937). These symptoms are believed to be caused by dimethylselenide in expired breath and may occur as a consequence of exposure to the expired breath of Se-intoxicated animals (Motley et al., 1937). Dimethylselenide, excreted solely by the lungs following relatively large doses of selenium, is considered responsible for the garlic breath experienced during Se intoxication (Diskin et al., 1979; Wilbur, 1980).

Chronic Se overexposure of dietary origin in humans was first examined in the rural areas of South Dakota and other plains regions where alkali disease had already been identified in animals (Smith and Westfall, 1937). Fifty families (100 subjects) with preliminary evidence of considerable Se absorption were chosen for investigation. Symptoms, including gastrointestinal disturbances, bad teeth, "icteroid" discoloration of the skin, and pallor, were noted in 76% of the group; however, the symptoms could not be conclusively identified as resulting directly from Se ingestion. Se intake was estimated to range from 0.01 to 0.2 mg/kg/day, with meat, eggs, and milk providing the largest source. Vegetables and well water were only secondary and variable sources of dietary Se in this study.

Subsequent to the description of alkali disease in South Dakota, Byers (1937) investigated an area in Mexico where the human and animal populations had very similar symptoms to those in seleniferous regions. The illness was known locally as "Soliman" disease and believed to be the result of mercury chloride poisoning from area mines. Analysis of soil and crop samples indicated very high levels of Se (up to 120 ppm in common mustard plants), apparently deposited as a waste product of nearby mines. Health studies of affected individuals were not reported.

[**] R.M. Jacobs, Ph.D., is a Supervisory Chemist with the Food and Drug Administration, San Francisco, CA.

In 1962, a family of Ute Indians near Ignacio, Colorado were reportedly poisoned by excessive Se in drinking well water (Anon., 1962). The well water, used for household purposes for 3 months, contained approximately 9 ppm Se. Symptoms of the family included hair loss, weakened nails, and listlessness.

Continuing investigations in South Dakota in later years (Howe, 1979) indicated that mean blood Se levels of presumed healthy blood donors were higher (0.265 ug/ml) than those reported by Allaway et al. (1968) (0.206 ug/ml) in a study of many locations throughout the United States. With some exceptions, the highest blood Se levels tended to be in regions where animal selenosis had been previously observed. The authors could not conclude, however, that even the highest blood Se concentration obtained in this study (0.60 ug/ml) was diagnostic of Se toxicosis.

Studies of possible Se intoxication have also been conducted in a seleniferous zone of Venezuela (Jaffee et al., 1972). Clinical and biochemical evaluations were performed on 11 children from Villa Bruzual, including height, weight, teeth, skin, hair, blood and urine Se, hemoglobin, hematocrit, glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alkaline phosphatase, prothrombin-time and urine creatinine. Food consumption patterns and degree of intestinal parasitism were also evaluated. Results from this population were compared with 50 children from Caracas. Mean blood selenium levels were 0.813 ug/ml and 0.355 ug/ml for children from Villa Bruzual and Caracas, respectively. Blood and urine Se levels were highest in those children who consumed the most home-grown foods. Clinical signs (nausea, vomiting, skin discoloration, loose hair, and pathological nails) were evident in more children in Villa Bruzual than in Caracas, however, biochemical differences between groups (other than Se levels) were not observed. The authors concluded that differences in clinical signs may have been the result of lower nutritional status and greater parasitic infestation in children from Villa Bruzual compared with those from Caracas, and not evidence of selenosis.

Perhaps the best evidence of endemic human disease resulting from both deficiency and toxicity of Se is from China. China is known to have the greatest variation of Se intakes, with average estimates ranging, throughout the country, from 11 to 4990 ug/person/day (Combs and Combs, 1984). Keshan and Kaschin-Beck diseases, syndromes believed to result in part from Se deficiency, have been discussed in section IV. A toxicity syndrome apparently resulting from excessive Se was reported in another province of China.

In the 1960's, a disease of unknown etiology, characterized by hair and nail loss, occurred in the Enshi county, Hubei Province, China (PRC). Residents of affected villages were evacuated, and most recovered soon after their diets were altered [reported in Yang et al., 1983]. Corn was identified as the toxic dietary constituent and subsequent analysis indicated that Se was responsible for the clinical syndrome. Identification of this problem prompted further studies in the area (Yang et al., 1983). Selenosis was defined in the population by the loss of hair and nails. In affected individuals, hair was brittle and easily broken; new hair lacked pigment. Nails were brittle with white spots and longitudinal streaks; they eventually broke off. Eruptive skin lesions were noted with reddish pigmentation frequently remaining after the lesions had healed. Tooth mottling was evident in approximately one-third of the cases, but this could not be distinguished from fluorosis which was also reported in the area. Numerous neurological signs (including, parethesias, pain in the extremities, tendon hyperreflexia, convulsions, paralysis, motor disturbance, and hemiplegia), frequently accompanied by gastrointestinal disturbances, were observed in one village that had a particularly high prevalence of selenosis. One hemiplegic died.

Follow-up studies conducted 2, 12, and 13 years after the peak period of intoxication (1961-1964) compared the Se status of individuals in four geographic areas: i) a high-Se area where selenosis was common in livestock and signs occasionally occurred in humans, ii) a high-Se area without a history of selenosis in livestock or humans, iii) a Se-adequate area, and iv) an area of endemic Keshan disease (i.e., severely Se-deficient area) (Yang et al., 1983). Hair, blood, and urinary selenium levels were found to reflect the degree of exposure to Se with elevations of 30- to 100-fold in areas of chronic selenosis compared with Se-adequate areas.

The Se contents of cereal and vegetable crops were also markedly elevated in areas with a history of selenosis. The average intake of Se in this region was calculated to be 4.99 mg/day (range, 3.2 to 6.69 mg/day), compared with an estimated average of 0.75 mg/day (range, 0.24 to 1.51 mg/day) in the high-Se area without a history of selenosis and 0.115 mg/day in a Se adequate area. The estimated daily Se intake of persons in the high-Se areas with and without a history of selenosis were based on 6 and 3 individuals, respectively. Because of the very small samples size, the delay in analysis following the outbreak, and the different analytical methodologies used for Se analysis, it is very difficult to determine the likelihood of health risk from consumption of these levels of Se. The authors questioned whether the highest level of intake estimated in the high-Se region (3.2 to 6.69 mg/day) would have elicited the selenotic signs and symptoms described or whether additional factors such as protein deficiency may have been required to exhibit toxicity signs.

Although drinking water is usually a relatively insignificant source of the total daily intake of Se for humans, in the area with chronic selenosis, 11 water samples were found to contain an average Se content of 54 ug/l. Four of these samples (from a village with high prevalence of selenosis) averaged 139 ug/l in Se content. The authors concluded that, in the case of this episode of selenosis, while drinking water was still far less significant a source of selenium than the diet, this level of selenium in water undoubtedly contributed to the high selenium intakes experienced in this area. (Given the typical estimated water intake of 2 liters/day, 54-135 ug Se/l of water would provide 108 to 270 ug of Se to the total diet; or, 2-5.6% of the total dietary Se in that geographic area). Other selenium exposures (e.g., air) may have been elevated in this population as well.

As mentioned above, the authors described several exacerbating factors which may have contributed to this particular outbreak of selenosis: drought, leading to increased consumption of crops (e.g., corn and other vegetables) that typically accumulate higher levels of Se than rice, which was normally consumed; increased use of plant ash during that period to improve crop yields; and decreased protein intakes, leading to increased susceptibility to Se toxicity (Rosenfeld and Beath, 1946). Current agricultural policy in China, which may help to mitigate this problem in the future, encourages production and consumption of more types of foodstuffs and exchange of food products at local markets (Yang et al., 1983).

As mentioned previously, the ability of Se compounds to be absorbed dermally is not well known. Occupational dermal exposure to some Se compounds (e.g., Se dioxide, Se oxychloride, sodium selenite) has resulted in painful burning skin reactions, erythema, allergic dermatitis (Combs and Combs, 1986h), and urticaria (Glover, 1967). Animal data indicate that Se oxychloride and sodium selenite may be absorbed through the skin to some degree (Dudley, 1938; Dutkiewicz et al., 1972). Se (i.e., Se sulfide) present in antidandruff shampoos is considered relatively nontoxic (Frost and Lish, 1975), and only capable of penetrating though a scalp wound to cause a generalized toxic reaction (Shamberger, 1983c). Ransone et al. (1961) reported apparent Se toxicosis resulting from inappropriate use of a Se-medicated shampoo which was absorbed through a scalp lesion. A 46-year old women who used the shampoo 2 or 3 times weekly for 8 months to cure a scalp eruption developed several signs of Se intoxication including tremor, abdominal pain with vomiting, garlic breath odor, and a metallic taste in her mouth. Additionally, her urinary Se level measured 5 days after her last use of the product was 32 ug/ml (although markedly elevated, this level was considered an underestimate of the true value because of delay in collection and laboratory analysis). Treatment was of a supportive nature and the patient recovered completely within 10 days.

Inhalation toxicity studies of environmentally important Se compounds (e.g., selenate, selenomethionine) have not been found in the literature, however, Combs and Combs (1986h) discussed reports of accidental inhalation exposures in industrial workers. Signs and symptoms resulting from inhalation of a few Se compounds include running nose, coughing, headache, dizziness, and nausea, followed by conjunctivitis, rhinitis, bronchitis, and possibly, pulmonary edema (Combs and Combs, 1986h). As mentioned earlier, anecdotal reports indicate that inhalation of dimethyselenide may be responsible for various respiratory symptoms. Although the acute toxicity of dimethylselenide is known to be considerably less than that of selenite or selenate, when injected intraperitoneally (i.p.) or subcutaneously (s.c.) to laboratory animals (McConnell and Portman, 1952; Ostadalova and Babicky, 1980), data from acute i.p. or s.c. LD_{50} studies may not be useful for assessing the risk of chronic exposure to low or moderate levels of dimethylselenide via inhalation. Chronic toxicity of inhaled dimethylselenide, including any possible carcinogenic, mutagenic, or teratogenic effects, has not been evaluated.

In addition to symptoms of acute or chronic selenosis, per se, other diseases have also been suggested as resulting from excessive subclinical intakes of Se. Hadjimarkos (1973) reviewed several epidemiological and experimental animal studies that indicated excessive consumption of Se during tooth formation increases susceptibility to dental caries. Jaffe et al. (1972) found a lower prevalence of caries among residents of seleniferous areas of Venezuela compared with residents of a control (i.e., lower Se) area; however, this result was confounded by the known higher fluorine content in drinking water of seleniferous regions. Jacobs (personal communication) noted severe apparently spontaneous caries development in at least one person who consumed the Brite Years Se preparation that contained inadvertently high Se levels (see section VI.B). Other authors have failed to confirm a correlation between the incidence of dental caries and Se intake (NRC, 1983d); the issue remains unclear.

One anecdotal report has suggested an association between high levels of Se and the occurrence of amyotrophic lateral sclerosis (ALS). Kilness and

Hochberg (1977) reported a cluster of 4 cases of ALS in rural residents of a sparsely populated seleniferous region of west-central South Dakota. Responses to this paper (Kurland, 1977; Schwarz, 1977) pointed out that other clusters of ALS have been reported in areas where environmental selenium is apparently not excessive (Hochberg et al., 1974). Norris and U (1978) furthered the case for coincidental association by reporting that 19 of 20 patients with well-established ALS had urinary selenium levels in the lower half of the laboratories' range for unexposed persons. Thus, it appears unlikely at this time that excessive Se is a causative agent in the development of ALS.

C. Mutagenicity

In vitro and in vivo studies have indicated that selenite, and possibly selenate, may cause DNA damage (Hogberg and Alexander, 1986). Both oxidation states of Se have been shown to induce weak base-pair substitutions in *Salmonella* *typhimurium* and the rec-assay of *Bacillus* *subtilis* (Noda et al., 1979). Sister chromatid exchange has been induced by selenite in lymphocyte cultures in the presence of glutathione (Ray, 1984), indicating that biotransformation may be needed to express mutagenic activity (Hogberg and Alexander, 1986). High levels of selenite have been found to cause chromosomal aberrations and increase sister chromatid exchange in cultured hamster bone marrow cells (Norppa et al., 1980).

D. Carcinogenicity

Early studies with rats suggested that Se might induce or enhance the development of hepatic cirrhosis and carcinoma (Nelson, 1943; Volgarev and Tscherkes, 1967). Numerous experimental complications unrelated to Se cast doubt on these findings (Combs and Combs, 1986i). A later report suggested that selenate, but not selenite, might be tumorigenic and carcinogenic (Schroeder and Mitchener, 1971). Because selenate-fed rats in this experiment survived an average of 125 days longer than control rats, it has been proposed that these rats merely lived long enough to be at greater risk for development of tumors (Combs and Combs, 1986i). Evidence for the potential carcinogenicity of Se is very weak; the majority scientific opinion at this time holds that Se, as found in food and water, is not a carcinogenic risk to man (Combs and Combs, 1986i; Lafond and Calabrese, 1979; Frost and Lish, 1975; Scott, 1973; Newberne, 1985; Vernie, 1984). In fact, much of the current literature regarding Se points to potential cancer chemopreventive and other protective properties of the element (see section X).

E. Reproductive Toxicity

Excessive levels of Se are well known to have teratogenic potential in avian species (Franke and Tully, 1936; Gruenwald, 1958; Palmer et al., 1973), and have also been shown to decrease reproductive performance in pigs (10 ppm dietary Se) (Wahlstrom and Olson, 1959), sheep (Rosenfeld and Beath, 1964b), and rodents (as little as 2.5 ppm in drinking water has been shown to affect reproductive performance in a second generation of rats) (Franke and Potter, 1936; Yonemoto et al., 1983). These effects have included reduced fertility or conception rates, reduced litter size and/or weight, and increased neonatal death. Terata have been reported in the offspring of sheep grazing on seleniferous ranges (Rosenfeld and Beath, 1964b). Malformations in sheep occur most frequently in eyes and feet. This is similar to frequency of abnormalities found in chicks.

Substantive epidemiological studies of reproductive outcomes following excessive Se exposure in humans have not been conducted. Possible risks from occupational or dietary exposures have been noted, however. In a comparison study of residents of a rural community with a water supply that contained between 50 and 125 ug/l Se and a control group (from the same county) of residents with a different (non-seleniferous) water supply, a significant positive correlation ($r = 0.56$) was found between 24-hour urinary Se output and history of miscarriage ($p<0.002$) (Tsongas and Ferguson, 1977). However, this relationship was not confirmed in a follow-up study (NRC, 1983d). Robertson (1970) noted a high rate of miscarriage and one bilateral clubfoot in a small group of female laboratory workers exposed to sodium selenite. In that study, however, urinary selenium levels in the exposed women were similar to controls. Small sample size and the fact that other potential etiologic agents were not ruled out limit interpretation of this observation. Based on an evaluation of public health records, a National Research Council panel concluded that congenital malformations of infants were not correlated with Se exposure (NRC, 1983d). In contrast, studies with hamsters have indicated that Se may be able to offer protection from the teratogenic effects of cadmium and arsenic under certain conditions (Holmberg and Ferm, 1969).

F. Mechanism(s) of Toxicity

Although the toxic mechanism(s) of selenium are not well understood, it is believed that selenium exerts its toxic effects by inhibiting important thiol-sensitive enzymes, for example, fatty acid synthase (Martin, 1978). Another possible consequence of selenite intoxication may be metabolic imbalances resulting from depletion of NADPH. During the detoxification of selenite via glutathione reductase, NADPH is a necessary cofactor. If the intake of selenite is excessive, NADPH may become limiting (Martin, 1978).

G. Interactions that Affect Toxicity

As noted throughout this document, numerous exogenous factors may affect bioavailability, absorption, distribution, and excretion of Se. Therefore, many of these factors may ultimately mitigate or exacerbate Se toxicosis. Similarly, dietary Se in the diet may modify the potency of a number of other toxic agents.

Considerable effort has been made to identify substances that may suppress Se toxicity. A number of compounds have been shown to decrease the toxicity of Se in some way: vitamin E, antioxidants, high dietary protein, sulfur amino acids, linseed oil meal, lysine, fish meal, sulfate, arsenic, lead, mercury, copper, silver, and zinc (Combs and Combs, 1986d; Levander, 1971; Mykkanen and Humaloja, 1984; Parizek et al., 1980; Venogopal and Luckey, 1978). The mechanisms of these interactions are not well characterized, but include increasing the biliary excretion of Se, enhancing the binding of Se in tissues in (presumably) less toxic forms, and/or reducing tissue Se residues (Levander, 1972). Therefore, some conditions (e.g., high copper or silver diets) may lead to biochemical signs of Se depletion as Se is concomitantly elevated in hepatic tissue (Mills, 1981).

Se toxicity may be exacerbated by deficiencies of certain dietary constituents. Rats fed low-protein diets exhibited signs of toxicity at lower intakes of selenium than did rats fed higher levels of protein (Rosenfeld and Beath, 1946). Interactions appear to vary considerably according to the chemical form of the element (Mills, 1981).

VII. TREATMENT

Currently, a treatment for Se toxicity is not known, although removal of the subject from the source of Se is very important in selenosis. Bromobenzene, although hepatotoxic (Combs and Combs, 1986h), was reported in earlier literature as a possible treatment for Se poisoning (Rosenfeld and Beath, 1964c). Cyanide and arsenite have been documented as counteracting Se intoxication in laboratory animals, although these remedies have never been reported in humans (Hogberg and Alexander, 1986).

VIII. TYPICAL EXPOSURE LIMITS/BODY BURDEN/TOXIC LIMITS

As previously mentioned, Se is generally widespread in most environments and a required nutrient for humans and animals. One Maryland study estimated typical consumption of Se from food to be approximately 132 ug/day in adults; the intake of Se for a 6-month old child was estimated to be 28 ug/day (Levander, 1976b). Another recent study in a seleniferous region of South Dakota found typical Se consumption levels up to 590 ug/d in adults, without signs of toxicity (Longnecker et al., 1987). Sakurai and Tsuchiya (1975) have estimated that in some extreme fish-eating Japanese populations, Se consumption may reach 500 ug/d. Other estimates of Se intake in U.S. adults have ranged from 60-216 ug/d (Welsh et al., 1981). One individual from Southern California was known to ingest 600 Se ug/d (including supplementation) for 18 months without apparent ill-effect (Schrauzer and White, 1978). Nine Finnish neuronal ceroid lipofuscinosis patients were supplemented with 0.050 mg Se/kg body weight in the form of sodium selenite (equivalent to a dose of 3,500 ug/d) for more than one year; toxic signs were not seen (Westermarck, 1977). However, Yang et al., (1983) reported thickened nails and garlic odor of dermal excretions in an 62 year old man who consumed 2,000 ug/d sodium selenite as a supplement (approximately 1,000 ug/d Se).

The EPA drinking water limit for Se is currently set at 10 ppb; only 1 sample in 418 analyzed in 1975 exceeded this limit (U.S. EPA, 1980). Given the typical estimated water consumption for adults of approximately 2 liters/-day, drinking water containing 10 ppb Se would provide 20 ug Se/day to the diet.

The average body burden of Se has been estimated to be approximately 14.6 mg (Hammond and Beliles, 1980), with approximately 13 mg contained in soft tissue (Snyder et al., 1975). The distribution of Se within the body has been discussed previously (see section V.B).

At the time of the last issuance of the Recommended Dietary Allowances (RDA) (i.e., 1980), the Food and Nutrition Board, National Academy of Sciences, was unable to quantitate a human requirement for Se (NRC, 1980); instead, a range of 50 to 200 ug/day was suggested as "safe and adequate" for adults. Based on extrapolation to lower consumption levels, "safe and adequate" intakes of Se for infants and children under 6 years have been suggested as 10 to 40 ug/day and 20 to 120 ug/day, respectively. The exact safety margin for this recommendation is unknown; however, evaluation of literature values for apparently safe and toxic exposures can aid in interpretation of a given exposure situation.

IX. INDICATORS OF EXCESSIVE ACCUMULATION

Methods for evaluation of Se status in population groups have been discussed by Klasing and Pilch (1985), utilizing numerous excellent reviews as well as expert consultants in the subject matter. Significant portions of this section have been excerpted and edited from that document.

A. Indices

Indices of Se status have been well reviewed by Levander (1985, 1986).

Se Levels in Blood. The measurement of Se concentration in blood and blood components has been used to assess the long-term Se nutritional status of animals and human subjects. In rats, erythrocyte and plasma Se levels were found to be indicators of the Se content of muscle and liver, the major sites of storage (Levander, 1985). Se levels in serum or plasma respond more quickly than muscle levels to short-term shifts in Se intake (Levander, 1985).

Blood Se values reported for free-living populations vary widely by geographic area. Some of the greatest variation in blood Se levels have been reported in China: persons living in an area with endemic Keshan disease were reported to average 0.021 g Se/ml whole blood, while persons living in an area with a history of chronic selenosis were reported to average 3.2 g Se/ml whole blood (Yang et al., 1983). While these values may provide useful reference points for comparing widely divergent selenium exposures, they are not particularly useful for assessing physiological implications of smaller deviations in Se status (Levander, 1985). Wahlstrom et al. (1984) have shown that blood Se levels do not necessarily reflect chronic selenosis symptoms in swine fed 8 ppm dietary selenite. Of red, black, and white pigs fed the supplemental Se, all had similar blood Se levels but only red pigs showed toxicity signs, including posterior paralysis and separation of the hooves at the coronary band. Additionally, recent data indicate that plasma Se may not accurately reflect increased body Se burden following moderate to high consumption level of organic Se compounds (Mills, 1981), the typical forms found in foodstuffs. Allaway et al. (1968) have reported blood Se values to vary from 0.10 to 0.34 mg/l among free-living person in 19 different geographic areas of the United States; the overall mean was 0.206 mg Se/l.

Erythrocyte Se level can be an indicator of total body Se status in most individuals on relatively stable diets (Levander, 1985). However, Se levels do not change as rapidly in the erythrocytes as they do in the muscle pool during acute Se intoxication (Levander, 1985). Additionally, chronic toxicity studies indicate that erythrocyte Se levels may not be adequate for monitoring body burdens of organic Se compounds (McAdam and Levander, 1987). Serum or plasma Se levels provide a shorter-term index of Se status than does erythrocyte level, but has the advantage of a much simpler assay procedure (Levander, 1985).

Se Content of Other Tissues. Muscle biopsy directly assesses the Se content of a large (50% of total body Se), long-term pool (Levander, 1985), but is clearly not feasible for humans. Hair Se has been reported to be an excellent indicator of muscle and liver Se in rats and to correlate well with blood Se levels of persons in China (Chen et al., 1980; Levander, 1985). Standardization of the amount of hair sampled as well as the scalp site is important for reproducibility (Combs and Combs, 1986g). Certain conditions may decrease the usefulness of hair trace mineral analysis: the use of Se-containing shampoos and various hair treatments (e.g., coloring and "perming") may affect Se or other element content (Davies, 1982; Levander, 1985). Hair color may be another complicating variable; Se content is known to vary in the hair of different colored pigs (Wahlstrom et al., 1984). The hair of red pigs contained less Se than white and black pigs fed a basal diet supplemented with 8 ppm sodium selenite; blood Se levels did not differ between pigs of different colors. Whether color differences affect Se deposition in the hair of humans is unknown, although Schroeder et al. (1970) reported that hair samples obtained from 8 persons, aged 3.5 to 84 years, contained remarkably similar Se levels, regardless of hair color. Toenail Se, like hair Se, has been suggested as a noninvasive tissue for assay. Toenails may present fewer problems due to environmental contamination than hair (Morris et al., 1983). Se is incorporated into nails as they grow and clippings from all ten toes can reflect tissue Se status integrated over an extended, but ill-defined, period of time (Morris et al., 1983). However, little information on the relationship of toenail Se to total body Se has been published. Additionally, factors which may affect nail growth and thereby influence their selenium content have not been identified (Levander, 1985).

Se Excretion in Urine. Although Se exposure has been monitored in an industrial setting by measuring Se excretion in the urine (Glover, 1967), the Se content of random urine samples can be greatly affected by recent dietary intake and is susceptible to diurnal variation (Levander, 1985; Thomson, 1974; Palmquist et al., 1979). Additionally, urinary volume is affected by numerous factors which are difficult to control for during analysis (Levander, 1985). Thus, urinary Se concentration is not especially valuable as a status assessment tool (Combs and Combs, 1986g). Blood Se levels and 24-hour urinary Se excretion in New Zealanders were significantly correlated (Griffiths and Thomson, 1974); however, 24-hour urine samples are exceedingly difficult to obtain (Levander, 1985). Additionally, dietary Se intakes can vary dramatically from day to day and urinary Se may partially reflect these differences.

Thus, more than a single urinary value may be necessary to accurately indicate Se status.

Glutathione Peroxidase Activity. The activity of this selenoenzyme in whole blood, serum or plasma, erythrocytes, and platelets has been measured as a functional indicator of Se status. Good correlations between Se content and glutathione peroxidase (GSHpx) activity in tissues are generally found in populations of known low Se status (Rea et al., 1979). However, enzyme activity is probably near optimal in most North Americans; thus, its usefulness in differentiating various degrees of Se status is questionable (Levander, 1985). Additionally, hemoglobin appears to interfere with the assay procedure for GSHpx in blood (Levander, 1986).

B. Methods

Analysis of the Se content of biological materials has been reviewed by numerous authors including, Berman (1980), Hogberg and Alexander (1986), Shamberger (1983d), and Tolg (1984). Many techniques have been used for Se analysis including fluorimetry, neutron activation analysis (NAA), proton-induced X-ray emission (PIXE), mass spectrometry, and atomic absorption spectrometry (AAS). Most methods currently used for analysis of Se rely on acid digestion and conversion to a common valence state prior to determination of the total Se content (Hogberg and Alexander, 1986). The specific method chosen for Se analysis may depend on availability and cost of equipment as well as the desired detection limit. Regardless of method, strict quality assurance practices should be observed to insure validity of data (NRC, 1971).

C. Basis for Interpretative Criteria

Widely varying indicators of Se status are generally useful for determination of overtly deficient and selenotic states, although blood or tissue Se levels do not always reliably predict clinical signs of Se toxicity or deficiency (Levander, 1985; Burk, 1976). Smaller deviations in Se assessment measures have unknown physiological or toxicological significance (Levander, 1985). Because of the myriad of biological substances that are known to interact metabolically with Se at nutritional and/or toxicological levels, interpretation of indicators of Se status, especially those at less extreme values is very difficult (Levander, 1986). For example, blood Se levels may change significantly with age, pregnancy status, alcoholism, cardiovascular disease, cancer, Down Syndrome, and any of several other conditions (Delves, 1985). Thus, investigation of the Se status of a population requires thorough planning and reference to carefully matched control data (Levander, 1985; Delves, 1985).

D. Quality Assurance/Quality Control

Se analysis has proved arduous for many research and non-research laboratories. Difficulties have been experienced with both accuracy and precision of results (Hogberg and Alexander, 1986). An international survey of blood Se analyses reported interlaboratory coefficients of variation greater than 13% for all samples (Koh, 1984). Lack of effective quality control schemes was cited as the most likely cause of unsatisfactory results. Many difficulties arise because of the instability and volatility of Se compounds during sampling, storage, preparation, and analysis (Hogberg and Alexander, 1986). Inadequate or too rapid destruction of organic matrices prior to analysis is another common source of error in some procedures, although newer methods help to reduce this problem (Krynitsky, 1987). Se is rapidly lost from a sample if charring occurs.

X. SPECIAL CONSIDERATIONS

As mentioned previously, Se is an essential nutrient; adequate consumption of this element is important for protection of human and animal health. In addition to known nutritional functions, studies with animal models suggest that Se may be a cancer or cardiovascular disease preventive agent at levels in clear excess of physiological requirements. Antineoplastic activity of selenium has been reported for a variety of chemically-induced cancers of the skin, liver, and colon, as well as chemically and virally-induced mammary neoplasia (Clark, 1985; Combs and Clark, 1985; Helzlsouer, 1983; Ip, 1986; Kok et al., 1985; Milner, 1985; Newberne, 1985; Salonen, 1986; Salonen and Huttunen, 1986; Scott, 1973; Vernie, 1984; Whanger, 1983). Although ecologic studies have generally shown similar inverse associations between regional distribution patterns for Se and age-specific death rates for various coronary, hypertensive, and cerebrovascular diseases (Mahan and Moxon, 1978; Shamberger et al., 1975), these, and other, correlational studies are subject to numerous confounding biases.

References

Abu-Erreish, G.M.; Whitehead, E.I.; Olson, O.E. 1968. Evolution of volatile selenium from soils. Soil Sci. 106:415-420.

Allaway, W.H. 1968. Control of the environmental levels of selenium. Trace Sub. Environ. Hlth. 2:181-206.

Allaway, W.H.; Kubota, J.; Losee, F.; Roth, M. 1968. Selenium, molybdenum, and vanadium in human blood. Arch. Environ. Hlth. 16:343-348.

Ancizar-Sordo, J. 1947. Occurrence of selenium in soils and plants of Colombia, South America. Soil Sci. 63:437-438.

Anon. 1962. Selenium poisons Indians. Sci. News Lett. 81:254.

Aronow, L.; Kerdel-Vegas, F. 1965. Seleno-cystathionine, a pharmacologically active factor in the seeds of Lecythis ollaria. Cytotoxic and depilatory effects of extracts of Lecythis ollaria. Nature 205:1185-1186.

Baird, R.B.; Pourian, S.; Gabrielian, S.M. 1972. Determination of trace amounts of selenium in wastewaters by carbon rod atomization. Anal. Chem. 44:1887-1889.

Berman, E. 1980. Selenium. In: Toxic metals and their analysis. Berman, E., ed. Philadelphia: Heyden & Son, Ltd. p.183,190.

Bopp, B.A.; Sonders, R.C.; Kesterson, J.W. 1982. Metabolic fate of selected selenium compounds in laboratory animals and man. Drug Metab. Rev. 13:271-318.

Brown, D.G.; Burk, R.F.; Seely, R.J.; Kiker, K.W. 1972. Effect of dietary selenium on the gastrointestinal absorption of $^{75}SeO_3$ in the rat. Internat. J. Vit. Nutr. Res. 42:588-591.

Buell, D.N. 1983. Potential hazards of selenium as a chemopreventive agent. Sem. Oncol. 10:311-321.

Bunce, G.E.; Hess, J.L. 1981. Biochemical changes associated with selenite-induced cataract in the rat. Exp. Eye Res. 33:505-514.

Burk, R.F. 1974. In vivo ^{75}Se binding to human plasma proteins after administration of $^{75}SeO_3$. Biochim. Biophys. Acta. 372:255-265.

Burk, R.F. 1976. The significance of selenium levels in blood. In: Proceedings of the symposium on selenium-tellurium in the environment, May 11-13, Notre Dame, IN. Available from: Center for Continuing Education, Notre Dame, IN. p.194-203.

Burk, R.F. 1984. Selenium. In: Present knowledge in nutrition. 5th Ed., Olson, R.E., ed., Washington, D.C.: The Nutrition Foundation, Inc. p.519-527.

Byers, H.G. 1937. Selenium in Mexico. Indust. Eng. Chem. 29:1200-1202.

Carson, B.L. 1986. Selenium. In: Toxicology and biological monitoring of metals in humans. Chelsea, MI: Lewis Publishers, Inc. p.213-217.

Carter, R.F. 1966. Acute selenium poisoning. Med. J. Aust. 1:525-528.

Cary, E.E.; Wieczorek, G.A.; Allaway, W.H. 1967. Reactions of selenite-selenium added to soils that produce low-selenium forages. Soil Sci. Soc. Amer. Proc. 31:21-26.

Cary, E.E.; Allaway, W.H.; Miller, M. 1973. Utilization of different forms of dietary selenium. J. Anim. Sci. 36:285-292.

Chau, Y.K.; Wong, P.T.S.; Silverberg, B.A.; Luxon, P.L.; Bengert, G.A. 1976. Methylation of selenium in the aquatic environment. Science 192:1130-1131.

Chen, X.; Yang, G.; Chen, J.; Chen, X.; Wen, Z.; Ge, K. 1980. Studies on the relations of selenium and Keshan disease. Biol. Trace Elem. Res. 2:91-107.

Civil, I.D.S.; McDonald, M.J.A. 1978. Acute selenium poisoning: Case report. NZ Med. J. 87:354-356.

Clark, L.C. 1985. The epidemiology of selenium and cancer. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:2584-2589.

Combs, G.F., Jr.; Clark, L.C. 1985. Can dietary selenium modify cancer risk? Nutr. Rev. 43:325-331.

Combs, G.F., Jr.; Combs, S.B. 1984. The nutritional biochemistry of selenium. Ann. Rev. Nutr. 4:257-280.

Combs, G.F., Jr.; Combs, S.B. 1986a. Chemical aspects of selenium. In: The role of selenium in nutrition. Ch. 1. Orlando, FL: Academic Press, Inc. p.1-14.

Combs, G.F., Jr.; Combs, S.B. 1986b. Selenium in the environment. In: The role of selenium in nutrition. Ch. 2. Orlando, FL: Academic Press, Inc. p.15-40.

Combs, G.F.; Jr.; Combs, S.B. 1986c. Selenium in foods and feeds. In: The role of selenium in nutrition. Ch. 3. Orlando, FL: Academic Press, Inc. p.41-126.

Combs, G.F., Jr.; Combs, S.B. 1986d. The biological availability of selenium in foods and feeds. In: The role of selenium in nutrition. Ch. 4. Orlando, FL: Academic Press, Inc. p.127-177.

Combs, G.F., Jr.; Combs, S.B. 1986e. Absorption, excretion, and metabolism of selenium In: The role of selenium in nutrition. Ch. 5. Orlando, FL: Academic Press, Inc. p.179-204.

Combs, G.F., Jr.; Combs, S.B. 1986f. Biochemical functions of selenium. In: The role of selenium in nutrition. Ch. 6. Orlando, FL: Academic Press, Inc. p.205-263.

Combs, G.F., Jr.; Combs, S.B. 1986g. Selenium in human nutrition and health. In: The role of selenium in nutrition. Ch. 8. Orlando, FL: Academic Press, Inc. p.327-399.

Combs, G.F., Jr.; Combs, S.B. 1986h. Effects of selenium excesses. In: The role of selenium in nutrition. Ch. 11. Orlando, FL: Academic Press, Inc. p.463-525.

Combs, G.F., Jr.; Combs, S.B. 1986i. Selenium and cancer. In: The role of selenium in nutrition. Ch. 10. Orlando, FL: Academic Press, Inc. p.413-461.

Cooper, W.C. 1967. Selenium toxicity in man. In: Symposium: Selenium in biomedicine. Muth, O.H.; Oldfield, J.E.; Weswig, P.H. eds. Westport, CT: The AVI Publishing Company, Inc.
p. 185-199.

Cummins, L.M.; Kimura, E.T. 1971. Safety evaluation of selenium sulfide antidandruff shampoos. Toxicol. Appl. Pharmacol. 20:89-96.

Davies, T.S. 1982. Hair analysis and selenium shampoos. Lancet 2:935.

Delves, H.T. 1985. Assessment of trace element status. Clin. Endocrin. Metab. 14:725-760.

Demayo, A.; Taylor, M.C.; Reeder, S.W. 1979. Guidelines for surface water quality. Vol. 1. Inorganic chemical substances. Selenium. Ottawa, Canada: Inland waters directorate. 21p.

Diplock, A.T. 1976. Metabolic aspects of selenium action and toxicity. Crit. Rev. Toxicol. 4:271-329.

Diskin, C.J.; Tomasso, C.L.; Alper, J.C.; Glaser, M.L.; Fliegel, S.E. 1979. Long-term selenium exposure. Arch. Intern. Med. 139:824-826.

Ducloux, J. Ph.; Ducloux, B.; Frantz, P.; Vincent, V. 1977. Recording a selenium intoxication. Review of the literature, Acta Pharmacol. Toxicol. 41:427-433.

Dudley, H.C. 1938. Toxicology of selenium. V. Toxic and vesicant properties of selenium oxycholoride. US Publ. Hlth. Serv. Publ. Hlth. Rep. 53:94-98.

Dutkiewicz, T.; Dutkiewicz, B.; Balcerska, I. 1972. Dynamics of organ and tissue distribution of selenium after intragastric and dermal administration of sodium selenite. Chem. Abs. 77:1476.

Eisler, R. 1985. Selenium hazards to fish, wildlife, and invertebrates: A synoptic review. U.S. Fish Wildlife Serv. Biol. Rep. 85(1.5). 57p.

Fan, A.M.; Book, S.A.; Neutra, R.R.; Epstein, D.M. 1988. Selenium and human health implications in California's San Joaquin Valley. J. Toxicol. Environ. Hlth. 23:539-559.

FDA Drug Bulletin. 1984. Toxicity with superpotent selenium. 14:19.

Fox, M.R.S; Jacobs, R.M. 1986. Human nutrition and metal ion toxicity. In: Metal ions in biological systems. Vol 20. New York: Marcel Dekker, Inc.

Franke, K.W. 1934a. A new toxicant occurring naturally in certain samples of plant foodstuffs. I. Results obtained in preliminary feeding trials. J. Nutr. 8:597-608.

Franke, K.W. 1934b. A new toxicant occurring naturally in certain samples of plant foodstuffs. II. The occurrence of the toxicant in the protein fraction. J. Nutr. 8:609-613.

Franke, K.W.; Potter, V.R. 1936. The effect of selenium containing foodstuffs on growth and reproduction of rats at various ages. J. Nutr. 12:205-214.

Franke, K.W.; Tully, W.C. 1936. A new toxicant occurring naturally in certain samples of plant foodstuffs. VII. Low hatchability due to deformities in chicks produced from eggs obtained from chickens of known history. Poultry Sci. 15:316-318.

Frost, D.V.; Lish, P.M. 1975. Selenium in biology. Annu. Rev. Pharmacol. 15:259-284.

Ganther, H.E. 1979. Metabolism of hydrogen selenide and methylated selenides. Adv. Nutr. Res. 2:107-128.

Ganther, H.E. 1986. Pathways of selenium metabolism including respiratory excretory products. J. Am. Coll. Toxicol. 5:1-5.

Geering, H.R.; Cary, E.E.; Jones, L.H.P.; Allaway, W.H. 1968. Solubility and redox criteria for the possible forms of selenium in soils. Soil. Sci. Soc. Amer. Proc. 32:35-40.

Gissel-Nielsen, G. 1971. Influence of pH and texture of the soil on plant uptake of added selenium. J. Agr. Food Chem. 19:1165-1167.

Glover, J.R. 1967. Selenium in human urine: A tentative maximum allowable concentration for industrial and rural populations. Ann. Occup. Hyg. 10:3-14.

Griffiths, N.M.; Stewart, R.D.H.; Robinson, M.F. 1976. The metabolism of [^{75}Se]selenomethionine in four women. Br. J. Nutr. 35:373-382.

Griffiths, N.M.; Thomson, C.D. 1974. Selenium in whole blood of New Zealand residents. NZ Med. J. 80:199-202.

Gruenwald, P. 1958. Malformations caused by necrosis in the embryo. Illustrated by the effect of selenium compounds on chick embryos. Am. J. Pathol. 34:77-95.

Hadjimarkos, D.M. 1973. Selenium in relation to dental caries. Fd. Cosmet. Toxicol. 11:1083-1095.

Hamilton, A. 1925. Industrial poisons in the United States. New York: MacMillan Co.

Hammond, P.B.; Beliles, R.P. 1980. Metals. In: Casarett and Doull's Toxicology. The basic science of poisons. Doull, J.; Klaassen, C.D.; Amdur, M.O. eds. New York: Macmillan Publishing Co., Inc. p.409-467.

Helzlsouer, K.J. 1983. Selenium and cancer prevention. Sem. Oncol. 10:305-310.

Helzlsouer, K.; Jacobs, R.; Morris, S. 1985. Acute selenium intoxication in the United States. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:1670.

Hochberg, F.H.; Bryan, J.A. II.; Whelan, M.A. 1974. Clustering of amyotrophic lateral sclerosis. Lancet 1:34.

Hogberg, J.; Alexander, J. 1986. Selenium. In: Handbook on the toxicology of metals. Ch. 19. Friberg, L.: Nordberg, G.F.; Vouk, V., eds. Amsterdam: Elsevier Science Publishers p.482-520.

Holmberg, R.E., Jr.; Ferm, V.H. 1969. Interrelationships of selenium, cadmium, and arsenic in mammalian teratogenesis. Arch. Environ. Hlth. 18:873-877.

Howe, S.M. 1979. Selenium in the blood of South Dakotans. Arch. Environ. Hlth. 34:444-448.

Ip, C. 1986. The chemopreventive role of selenium in carcinogenesis. J. Am. Coll. Toxicol. 5:7-19.

Jaffe, W.G.; Ruphael, M.D.; Mondragon, M.C.; Cuevas, M.A. 1972. Clinical and biochemical study in children from a seleniferous zone. Arch. Latinoamer. Nutr. 22:595-611.

Janghorbani, M.; Christensen, M.J.; Nahapetian, A.; Young, V.R. 1982. Selenium metabolism in healthy adults: quantitative aspects using the stable isotope $^{74}SeO_3$. Am. J. Clin. Nutr. 35:647-654.

Jensen, R.; Closson, W.; Rothenberg, R. 1984. Selenium intoxication - New York. J. Am. Med. Assoc. 251:1938.

Jereb, M.; Falk, R.; Jereb, B.; Lindhe, C. 1975. Radiation dose to the human body from intravenously administered ^{75}Se-sodium selenite. J. Nucl. Med. 16:846-850.

Johnson, R.A.; Baker, S.S.; Fallon, J.T.; Maynard, E.P., III; Ruskin, J.N.; Wen, Z.; Ge, K.; Cohen, H.J. 1981. An occidental case of cardiomyopathy and selenium deficiency. N. Engl. J. Med. 304:1210-1212.

Kerdel-Vegas, F. 1964. Generalized hair loss due to the ingestion of "coco de mono" (Lecythis ollaria). J. Invest. Dermatol., 42:91-94.

Kerdel-Vegas, F.; Wagner, F.; Russell, P.B.; Grant, N.H.; Alburn, H.E.; Clark, D.E.; Miller, J.A. 1965. Structure of the pharmacologically active factor in the seeds of Lecythis ollaria. Nature 205:1186-1187.

Kilness, A.W.; Hochberg, F.H. 1977. Amyotrophic lateral sclerosis in a high selenium environment. J. Am. Med. Assoc. 237:2843-2844.

Klasing, S.A.; Pilch, S.M. 1985. Selenium. In: Suggested measures of nutritional status and health conditions for the third National Health and Nutrition Examination Survey. Prepared for the Food and Drug Administration under contract No. FDA 223-84-2059 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD. Available from: FASEB Special Publications Office, Bethesda, MD. p.142-150.

Koh, T.-S. 1984. An interlaboratory survey of the determination of selenium in blood: A preliminary report. In: Trace element-analytical chemistry in medicine and biology. vol. 3. Bratter, P.; Schramel, P. eds. New York: Walter de Gruyter. p.201-206.

Kok, F.J.; Hofman, A.; Vandenbroucke, J.P.; Valkenburg, H.A. 1985. Selenium and cardiovascular disease. Int. J. Epidemiol. 14:335.

Koppel, C.; Baudisch, H.; Beyer, K.-H.; Kloppel, I.; Schneider, V. 1986. Fatal poisoning with selenium dioxide. Clin. Toxicol. 24:21-35.

Krynitsky, A.J. 1987. Preparation of biological tissue for determination of arsenic and selenium by graphite furnace atomic absorption spectrometry. Anal. Chem. 59:1884-1886.

Kurland, L.T. 1977. Amyotrophic lateral sclerosis and selenium. J. Am. Med. Assoc. 238:2365-2366.

Lafond, M.G.; Calabrese, E.J. 1979. Is the selenium drinking water standard justified? Med. Hypoth. 5:877-899.

Lathrop, K.A.; Johnston, R.E.; Blau, M.; Rothschild, E.O. 1972. Radiation dose to humans from ^{75}Se-L-selenomethionine. J. Nucl. Med. 13 (Suppl 6):10-30.

Letey, J.; Roberts, C.; Penberth, M.; Vasek, C. 1986. An agricultural dilemma: drainage water and toxics disposal in the San Joaquin Valley. Oakland, CA: The Regents of the University of California. 56p.

Levander, O.A. 1971. Factors that modify the toxicity of selenium. In: Newer trace elements in nutrition. Ch. 5. Mertz, W.; Cornatzer, W.E. eds. New York: Marcel Dekker, Inc. p.57-83.

Levander, O.A. 1972. Metabolic interrelationships and adaptations in selenium toxicity. Ann. NY Acad. Sci. 192:181-192.

Levander, O.A. 1976a. Selected aspects of the comparative metabolism and biochemistry of selenium and sulfur. In: Trace elements in human health and disease. Vol. 2. Prasad, A.S. ed. New York: Academic Press. p.135-163.

Levander, O.A. 1976b. Selenium in foods. In: Proceedings of the symposium on selenium-tellurium in the environment, May 11-13, Notre Dame IN. Available from: Center for Continuing Education, Notre Dame, IN. p.26-53.

Levander, O.A. 1985. Considerations on the assessment of selenium status. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:2579-2583.

Levander, O.A. 1986. The need for measures of selenium status. J. Am. Coll. Toxicol. 5:37-42.

Levander, O.A.; Argrett, L.C. 1969. Effects of arsenic, mercury thallium, and lead on selenium metabolism in rats. Toxicol. Appl. Pharmacol. 14:308-314.

Levander, O.A.; Baumann, C.A. 1966a. Selenium metabolism. V. Studies on the distribution of selenium in rats given arsenic. Toxicol. Appl. Pharmacol. 9:98-105.

Levander, O.A.; Baumann, C.A. 1966b. Selenium metabolism. VI. Effect of arsenic on the excretion of selenium in the bile. Toxicol. Appl. Pharmacol. 9:106-115.

Levander, O.A.; Sutherland, B.; Morris, V.C.; King, J.C. 1981. Selenium metabolism in human nutrition. In: Selenium in biology and medicine. Spallholz, J.E.; Martin, J.L.; Ganther, H.E. eds. Westport, CT: AVI Publishing Company, Inc. p.256-268.

Longnecker, M.P.; Taylor, P.R.; Levander, O.A.; Howe, S.M.; Veillon, C.; McAdam, P.A.; Patterson, K.Y.; Holden, J.M.; Stampfer, M.J.; Morris, S.J; Willett, W.C. 1987. Tissue selenium (Se) levels and indices of Se exposure in a seleniferous area. Fed. Proc. Fed. Am. Soc. Exp. Biol. 46:587.

Magos, L.; Tandon, S.K.; Webb, M.; Snowden, R. 1987. The effects of treatment with selenite before and after the administration of [^{75}Se]selenite on the exhalation of [^{75}Se]dimethylselenide. Toxicol. Lett. 36:167-172.

Mahan, D.C.; Moxon, A.L. 1978. Effects of adding inorganic or organic selenium sources to the diets of young swine. J. Anim. Sci. 47:456-466.

Martin, J.L. 1978. Nutrient toxicities in animals and man: Selenium. In: CRC Handbook series in nutrition and food. Section E, Nutritional disorders. Vol. 1. p.309-317.

Martin, J.L.; Gerlach, M.L. 1972. Selenium metabolism in animals. Ann. NY Acad. Sci. 192:193-199.

Matoba, R.; Kimura, H.; Uchima, E.; Abe, T.; Yamada T.; Mitsukuni, Y.; Shikata, I. 1986. An autopsy case of acute selenium (selenious acid) poisoning and selenium levels in human tissues. Forensic Sci. Int. 31:87-92.

McAdam, P.A.; Levander, O.A. 1987. Chronic toxicity and retention of dietary selenium fed to rats as D- or L-selenomethionine, selenite, or selenate. Nutr. Res. 7:601-610.

McConnell, K.P.; Portman, O.W. 1952. Toxicity of dimethyl selenide in the rat and mouse. Proc. Soc. Exp. Biol. Med. 79:230-231.

McConnell, K.P.; Roth, D.M. 1966. Respiratory excretion of selenium. Proc. Soc. Exp. Biol. Med. 123:919-921.

McCoy, K.E.M.; Weswig, P.H. 1969. Some selenium responses in the rat not related to vitamin E. J. Nutr. 98:383-389.

Medinsky, M.A.; Cuddihy, R.G.; McClellan, R.O. 1981. Systemic absorption of selenious acid and elemental selenium aerosols in rats. J. Toxicol. Environ. Hlth. 8:917-928.

Mills, C.F. 1981. Interactions between elements in tissues: Studies in animal models. Fed. Proc. Fed. Am. Soc. Exp. Biol. 40:2138-2143.

Milner, J.A. 1985. Selenium and carcinogenesis. In: Xenobiotic metabolism: Nutritional effects. ACS Symposium Series. No. 277. Finley, J.W.; Schwass, D.E. eds. American Chemical Society. p.267-282.

Morris, J.S.; Stampfer, M.J.; Willett, W. 1983. Dietary selenium in humans. Toenails as an indicator. Biol. Trace Elem. Res. 5:529-537.

Motley, H.L.; Ellis, M.M.; Ellis, M.D. 1937. Acute sore throats following exposure to selenium. J. Am. Med. Assoc. 109:1718-1719.

Mutanen, M. 1986. Bioavailability of selenium. Ann. Clin. Res. 18:48-54.

Muth, O.H.; Oldfield, J.E.; Remmert, L.F.; Schumer, J.R. 1958. Effects of selenium and vitamin E on white muscle disease. Science 128:1090.

Mykkanen, H.; Humaloja, T. 1984. Effect of lead on the intestinal absorption of sodium selenite and selenomethionine (^{75}Se) in chicks. Biol. Trace Elem. Res. 6:11-17.

National Research Council (NRC). 1971. Selenium in nutrition. Board on agriculture, committee on animal nutrition. Washington., DC: National Academy Press. 67p.

National Research Council (NRC). 1977. Inorganic solutes. In: Drinking water and health. Ch. 5. Washington, DC: National Academy Press. p.205-488.

National Research Council, Food and Nutrition Board. 1980. Recommended Dietary Allowances. 9th Rev. Washington, D.C.: National Academy Press. 185p.

National Research Council (NRC). 1983a. Chemistry. In: Selenium in nutrition. Ch. 2. Revised edition. Board on agriculture, committee on animal nutrition. Washington, DC: National Academy Press. p.3-9.

National Research Council (NRC). 1983b. Distribution. In: Selenium in nutrition. Ch. 3. Revised edition. Board on agriculture, committee on animal nutrition. Washington, DC: National Academy Press. p.10-39.

National Research Council (NRC). 1983c. Metabolism. In: Selenium in nutrition. Ch. 5. Revised edition. Board on agriculture, committee on animal nutrition. Washington, D.C.: National Academy Press. p.57-76.

National Research Council (NRC). 1983d. Selenium and human health. In: Selenium in nutrition. Ch. 8. Revised edition. Board on agriculture, committee on animal nutrition. Washington, DC: National Academy Press. p.114-132.

Nelson, A.A.; Fitzhugh, O.G.; Calvery, H.O. 1943. Liver tumors following cirrhosis caused by selenium in rats. Cancer Res. 3:230-236.

Nesheim, M.C.; Scott, M.L. 1959. Studies on the nutritive effects of selenium for chicks. J. Nutr. 65:601-618.

Newberne, P.M. 1985. The influence of nutrition, immunologic status, and other factors on the development of cancer. In: Toxicological risk assessment. Vol. II. General criteria and case studies. Clayson, D.B.; Krewski, D.; Munro, I. eds. Boca Raton, FL: CRC Press. p.43-87.

Noda, M.; Takano, T.; Sakurai, H. 1979. Mutagenic activity of selenium compounds. Mutation Res. 66:175-179.

Norppa, H.; Westermarck, T.; Knuutila, S. 1980. Chromosomal effects of sodium selenite in vivo. III. Aberrations and sister chromatid exchanges in Chinese hamster bone marrow. Hereditas 93:101-105.

Norris, F.H., Jr.; U, K.S. 1978. Amyotrophic lateral sclerosis and low urinary selenium levels. J. Am. Med. Assoc. 239:404.

Obermeyer, B.D.; Palmer, I.S.; Olson, O.E.; Halverson, A.W. 1971. Toxicity of trimethylselenonium chloride in the rat with and without arsenite. Toxicol. Appl. Pharmacol. 20:135-146.

Olson, O.E. 1986. Selenium toxicity in animals with emphasis on man. J. Am. Coll. Toxicol. 5:45-70.

Ostadalova, I.; Babicky, A. 1980. Toxic effect of various selenium compounds on the rat in the early postnatal period. Arch. Toxicol. 45:207-211.

Ostadalova, I.; Babicky, A.; Obenberger, J. 1978. Cataract induced by administration of a single dose of sodium selenite to suckling rats. Experientia 34:222-223.

Ostadalova, I.; Babicky, A.; Obenberger, J. 1979. Cataractogenic and lethal effect of selenite in rats during postnatal ontogenesis. Physiol. Bohemoslov. 28:393-397.

Painter, E.P.; Franke, K.W. 1936. Selenium in proteins from toxic foodstuffs. II. The effect of acid hydrolysis. Cereal Chem. 13:122-139.

Palmer, I.S.; Arnold, R.L.; Carlson, C.W. 1973. Toxicity of various selenium derivatives to chick embryos. Poultry Sci. 52:1841-1846.

Palmquist, D.L.; Moxon, A.L.; Cantor, A.H. 1979. Pattern of urinary selenium excretion in normal adults. Fed. Proc. Fed. Am. Soc. Exp. Biol. 38:391.

Parizek, J.; Kalouskova, J.; Benes, J.; Pavlik, L. 1980. Interactions of selenium-mercury and selenium-selenium compounds. Ann. NY Acad. Sci. 355:347-360.

Patterson, E.L.; Milstrey, R.; Stokstad, E.L.R. 1957. Effect of selenium in preventing exudative diathesis in chicks. Proc. Soc. Exp. Biol. Med. 95:617-620.

Pentel, P.; Fletcher, D.; Jentzen, J. 1985. Fatal acute selenium toxicity. J. Forensic Sci. 30:556-562.

Peterson, P.J.; Butler, G.W. 1962. The uptake and assimilation of selenite by higher plants. Aust. J. Biol. Sci 15:126-146.

Presser, T.S.; Barnes, I. 1984. Selenium concentrations in waters tributary to and in the vicinity of the Kesterson National Wildlife Refuge, Fresno and Merced counties, California. Menlo Park, CA: U.S. Geological Survey. 26p.

Presser, T.S.; Barnes, I. 1985. Dissolved constituents including selenium in waters in the vicinity of Kesterson National Wildlife Refuge and the west Grassland, Fresno and Merced counties. Menlo Park, CA: U.S. Geological Survey. 73p.

Ransone, J.W.; Scott, N.M., Jr.; Knoblock, E.C. 1961. Selenium sulfide intoxication. New Eng. J. Med. 264:384-385.

Ray, J.H. 1984. Sister-chromatid exchange induction by sodium selenite: reduced gluthathione converts Na_2SeO_3 to its SCE-inducing form. Mutation Res. 141:49-53.

Rea, H.M.; Thomson, C.D.; Campbell, D.R.; Robinson, M.F. 1979. Relation between erythrocyte selenium concentrations and glutathione peroxidase (EC 1.11.1.9) activities of New Zealand residents and visitors to New Zealand. Br. J. Nutr. 42:201-208.

Robertson, D.S.F. 1970. Selenium - a possible teratogen? Lancet 1:518-519.

Robinson, J.R.; Robinson, M.F.; Levander, O.A.; Thomson, C.D. 1985. Urinary excretion of selenium by New Zealand and North American human subjects on differing intakes. Am. J. Clin. Nutr. 41:1023-1031.

Rosenfeld, I.; Beath, O.A. 1946. The influence of protein diets on selenium poisoning. I. Am. J. Vet. Res. 7:52-56.

Rosenfeld, I.; Beath, O.A 1964a. Accumulation of selenium by plants. In: Selenium. Geobotany, biochemistry, toxicity, and nutrition. Ch. 4. New York: Academic Press, Inc. p.91-140.

Rosenfeld, I.; Beath, O.A. 1964b. Selenium poisoning in animals. In: Selenium. Geobotany, biochemistry, toxicity, and nutrition. Ch. 5. New York: Academic Press, Inc. p.141-226.

Rosenfeld, I.; Beath, O.A. 1964c. Selenium in relation to public health. In: Selenium. Geobotany, biochemistry, toxicity, and nutrition. Ch. 8. New York: Academic Press, Inc. p.279-298.

Rotruck, J.T.; Pope, A.L.; Ganther, H.E.; Swanson, A.B.; Hafeman, D.G.; Hoekstra, W.G. 1973. Selenium: Biochemical role as a component of glutathione peroxidase. Science 179:588-590.

Sakurai, H.; Tsuchiya, K. 1975. A tentative recommendation for the maximum daily intake of selenium. Environ. Physiol. Biochem. 5:107-118.
Salonen, J.T. 1986. Selenium and human cancer. Ann. Clin. Res. 18:18-21.

Salonen, J.T.; Huttunen, J.K. 1986. Selenium in cardiovascular diseases. Ann. Clin. Res. 18:30-35.

Schellmann, B.; Raithel, H.J.; Schaller, K.H. 1986. Acute fatal selenium poisoning. Toxicological and occupational medical aspects. Arch. Toxicol. 59:61-63.

Schiavon, R.; Freeman, G.E.; Guidi, G.C.; Perona, G.; Zatti, M.; Kakkar, V.V. 1984. Selenium enhances prostacyclin production by cultured endothelial cells: Possible explanation for increased bleeding times in volunteers taking selenium as a dietary supplement. Thromb. Res. 34:389-396.

Schrauzer, G.N.; White, D.A. 1978. Selenium in human nutrition: Dietary intakes and effects of supplementation. Bioinorg. Chem. 8:303-318.

Schroeder, H.A.; Frost, D.V.; Balassa, J.J. 1970. Essential trace metals in man: Selenium. J. Chron. Dis. 23:227-243.

Schroeder, H.A.; Mitchener, M. 1971. Selenium and tellurium in rats: Effect on growth, survival and tumors. J. Nutr. 101:1531-1540.

Schwarz, K. 1977. Amyotrophic lateral sclerosis and selenium. J. Am. Med. Assoc. 238:2365.

Schwarz, K.; Bieri, J.G.; Briggs, G.M.; Scott, M.L. 1957. Prevention of exudative diathesis in chicks by factor 3 and selenium. Proc. Soc. Exp. Biol. Med. 95:621-625.

Schwarz, K.: Foltz, C.M. 1957. Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. J. Am. Chem. Soc. 79:3292-3293.

Scott, M.L. 1973. The selenium dilemma. J. Nutr. 103:803-810.

Shamberger, R.J. 1983a. Metabolism of selenium. In: Biochemistry of selenium. Ch. 3. New York: Plenum Press. p.59-75.

Shamberger, R.J. 1983b. Environmental occurrence of selenium. In: Biochemistry of selenium. Ch. 6. New York: Plenum Press. p. 167-183.

Shamberger, R.J. 1983c. Toxicity of selenium: In: Biochemistry of selenium. Ch. 7. New York: Plenum Press. p.185-206.

Shamberger, R.J. 1983d. Analytical methods of selenium determination. In: Biochemistry of selenium. Ch. 10. New York: Plenum Press. p.311-327.

Shamberger, R.J.; Tytko, S.A.; Willis, C.E. 1975. Selenium and heart disease. Trace Sub. Environ. Hlth. 9:15-22.

Shrift, A.; Virupaksha, T.K. 1965. Seleno-amino acids in selenium-accumulating plants. Biochim. Biophys. Acta. 100:65-75.

Sioris, L.J.; Guthrie, K.; Pentel, P.R. 1980. Acute selenium poisoning. Vet. Hum. Toxicol. 22:364.

Smith, M.I.; Westfall, B.B. 1937. Further field studies on the selenium problem in relation to public health. Public Health Rep. 52:1375-1384.

Snodgrass, W.; Rumack, B.H.; Sullivan, J.B., Jr. 1981. Selenium: Childhood poisoning and cystic fibrosis. Clin. Toxicol. 18:211-220.

Snyder, W.S.; Cook, M.J.; Nasset, E.S.; Karhausen, L.R.; Howells, G.P.; Tipton, I.H. 1975. Report of the task group on reference man. International commission on radiological protection. No. 23. New York: Pergamon Press.

Sprinker, L.H.; Harr, J.R.; Newberne, P.M.; Whanger, P.D.; Weswig, P.H. 1971. Selenium deficiency lesions in rats fed vitamin E supplemented rations. Nutr. Rep. Inter. 4:335-340.

State Water Resources Control Board (SWRCB). 1987. Regulation of agricultural drainage to the San Joaquin River. SWRCB Order No. W.Q. 85-1. Technical Committee Report. Sacramento, CA: Available from State Water Resources Control Board. p.1-17.

Sunde, R.A.; Gutzke, G.E.; Hoekstra, W.G. 1981. Effect of dietary methionine on the biopotency of selenite and selenomethionine in the rat. J. Nutr. 111:76-86.

Thompson, J.N.; Scott, M.L. 1969. Role of selenium in the nutrition of the chick. J. Nutr. 97:335-342.

Thompson, J.N.; Scott, M.L. 1971. Impaired lipid and vitamin E absorption related to atrophy of the pancreas in selenium-deficient chicks. J. Nutr. 100:797-809.

Thomson C.D. 1974. Recovery of large doses of selenium given as sodium selenite with or without vitamin E. NZ Med. J. 80:163-168.

Thomson, C.D.; Stewart, R.D.H. 1974. The metabolism of [^{75}Se]selenite in young women. Br. J. Nutr. 32:47-57.

Tolg, G. 1984. Selenium-analysis in biological materials. In: Trace element-analytical chemistry in medicine and biology. Vol. 3. Bratter, P.; Schramel, P., ed. New York: Walter de Gruyter. P.95-125.

Trelease, S.F.; Di Somma, A.A.; Jacobs, A.L. 1960. Seleno-amino acid found in astragalus bisulcatus. Science 132:618.

Tsongas, T.A.; Ferguson, S.W. 1977. Human health effects of selenium in a rural Colorado drinking water supply. Trace Sub. Environ. Hlth. 11:30-35.

U.S. Environmental Protection Agency. 1980. Ambient water quality criteria for selenium. Springfield, VA: National Technical Information Service. PB81-117814.

U.S. Environmental Protection Agency. 1982. Fate of priority pollutants in publicly owned treatment works. Vol. I. EPA 440/1-82/303.

van Rij, A.M.; Thomson, C.D.; McKenzie, J.M.; Robinson, M.F. 1979. Selenium deficiency in total parenteral nutrition. Am. J. Clin. Nutr. 32:2076-2085.

Venugopal, B.; Luckey, T.D. 1978. Toxicity of group VI metals and metalloids. In: Metal toxicity in mammals. Vol. 2. Chemical toxicity of metals and metalloids. Ch. 6. New York: Plenum Press. p.234-245.

Vernie, L.N. 1984. Selenium in carcinogenesis. Biochim. Biophys. Acta 738:203-217.

Volgarev, M.N.; Tscherkes, L.A. 1967. Further studies in tissue changes associated with sodium selenate. In: Selenium in biomedicine. Muth, O.H. ed. AVI Publishing Co., Inc.: Westport, CT. p.179-184.

Wahlstrom, R.C.; Olson, O.E. 1959. The effect of selenium on reproduction in swine. J. Anim. Sci. 18:141-145.

Wahlstrom, R.C.; Goehring, T.B.; Johnson, D.D.; Libal, G.W.; Olson, O.E.; Palmer, I.S.; Thaler, R.C. 1984. The relationship of hair color to selenium content of hair and selenosis in swine. Nutr. Rep. Inter. 29:143-147.

Welsh, S.O.; Holden, J.M.; Wolf, W.R.; Levander, O.A. 1981. Selenium in self-selected diets of Maryland residents. J. Am. Diet. Assoc. 79:277-285.

Westermarck, R. 1977. Selenium content of tissues in Finnish infants and adults with various diseases, and studies on the effects of selenium supplementation in neuronal ceroid lipofuscinosis patients. Acta Pharm. Toxicol. 41:121-128.

Whanger, P.D.; Pedersen, N.D.; Hatfield, J.; Weswig, P.H. 1976. Absorption of selenite and selenomethionine from ligated digestive tract segments in rats. Proc. Soc. Exp. Biol. Med. 153:295-297.

Whanger, P.D. 1983. Selenium interactions with carcinogens. Fund. Appl. Toxicol. 3:424-430.

Wilber, C.G. 1980. Toxicology of selenium: a review. Clin. Toxicol. 17:171-230.

Willett, W.C.; Polk, B.F.; Morris, J.S.; Stampfer, M.J.; Pressel, S.; Rosner, B.; Taylor, J.O.; Schneider, K.; Hames, C.G. 1983. Prediagnostic serum selenium and risk of cancer. Lancet 2:130-134.

Yang, G.; Wang, S.; Zhou, R.; Sun, S. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37:872-881.

Yonemoto, J.; Satoh, H.; Himeno, S.; Suzuki, T. 1983. Toxic effects of sodium selenite on pregnant mice and modification of the effects by vitamin E or reduced glutathione. Teratol. 28:333-340.

Young, V.R.; Nahapetian, A.; Janghorbani, M. 1982. Selenium bioavailability with reference to human nutrition. Am. J. Clin. Nutr. 35:1076-1088.

Zieve, R.; Peterson, P.J. 1981. Factors influencing the volatilization of selenium from soil. Sci. Total Environ. 19:277-284.

Zieve, R.; Peterson P.J. 1984. Dimethylselenide - an important component of the biogeochemical cycling of selenium. Trace Sub. Environ. Hlth. 18:262-267.

APPENDIX B

BORON

I. INTRODUCTION

Boron has been identified as a potential substance-of-concern in agricultural drainage waters from the west side of the San Joaquin Valley and a serious water quality concern in the San Joaquin River (Hansen and Morehardt, 1987). Estimates of the highest median concentrations of boron in ground waters, surface runoff waters, and river water (7.4, 3.1, and 1.1 ppm, respectively) all exceed the established limits recommended to protect plant and aquatic life (Hansen and Morehardt, 1987).

II. OCCURRENCE

A. Natural

Boron is a trivalent metalloid comprising about 0.001% of the earth's crust in the form of its compounds, rather than in the elemental state (Windholz, 1976). More boron is contained in soils formed from marine sediments than those formed from igneous rocks, and soils on average have a higher content than rocks (Norrish, 1975). The forms of boron found in nature include boric acid (H_2BO_3), such as found in some volcanic spring waters, and various salts, primarily borax ($Na_2B_4O_7.10H_2O$) and colemanite ($Ca_2B_6O_{11}.5H_2O$) (Weast, 1983-1984). A native sodium tetraborate, from which borax is prepared, is found in California, Nevada, Oregon, and Asia Minor. Other naturally-occurring forms include boronatrocalcite ($CaB_4O_7NaBO_2.8H_2O$) and borocite ($Mg_7Cl_2B_{16}O_{30}$) (National Research Council, 1980). As noted by Sprague (1972), the ecological significance of boron is associated almost exclusively with boric acid and the borates. Other boron compounds are manufactured and used in small quantities under relatively controlled conditions. Upon release into the environment, most of these compounds break down to yield boric acid and borates. Boron is readily taken up by plants and is ubiquitous in animal tissues.

B. Anthropogenic

Boron compounds have a variety of industrial uses. Borax is widely employed as a cleaning product with soaps and detergents, and is an ingredient in some cosmetics (Windholz, 1976). Boron is used as a neutron absorber in nuclear chemistry and as a component of alloys to harden other metals (Berman, 1980). Boric acid, borax and other borates are variously employed in printing, dying, and photography; manufacturing glazes and enamels; weatherproofing wood; soldering metals; fireproofing fabrics; and curing skins (Berman, 1980). Boric oxide is used in metallurgy and boranes are used in rocket propellants and as catalysts for olefin polymerization.

Borax and boric acid are prior-sanctioned ingredients authorized for use in the manufacture of paper and paperboard products used in food packaging [21 CFR 181.30] and are also authorized as regulated indirect food additives when these compounds are used in packaging material in contact with food [21 CFR

175.105, 21 CFR 176.180] (Office of the Federal Register, 1980; Select Committee on GRAS Substances, 1980). Both borax and boric acid have been used as mild topical astringents and antiseptics for human and veterinary use (Windholz, 1976). Approximately 400 proprietary preparations available in the United States contain boric acid (Berman, 1980).

Boron is added frequently to fertilizers for plants with high requirements for this element, such as alfalfa, apples, and certain root and cruciferous vegetables (National Research Council, 1980). Borates, in high concentrations, have been used as nonselective herbicides. They may be applied singly, with sodium chlorate, or in combination with organic herbicides (where their biostatic effects reduce the microbial breakdown of the organic herbicide) (Sprague, 1972).

III. ENVIRONMENTAL FATE

A. Chemical Forms

Boron is the first, and most electronegative, of the Group III elements of the periodic table. Its chemistry more closely resembles that of carbon and silicon than that of the metallic Group III elements (Sprague, 1972). The electron structure of boron is $1s^2 2s^2 p$, thus, it usually forms three bonds to other elements. The vacant fourth orbital permits the formation of another bond by accepting the donation of an electron pair from another element (Sprague, 1972). Despite the potential diversity of its chemistry, naturally-occurring boron is limited to relatively few compounds because of the great stability of the boron-oxygen bond (Sprague, 1972).

Boric acid occurs as colorless, odorless, transparent crystals or a white granular powder; is soluble in water, ethanol, and glycerol; and is volatile with steam (Windholz, 1976). Borax is found as such or as a component of uxelite, colemanite, or kernite (Weast, 1983-1984). In its anhydrous form, it is a white crystalline substance; upon hydration it becomes a hard crystalline compound. Borax is soluble in water and glycerol, but not in alcohol (Windholz, 1976). Borax is representative of a large class of inorganic boron compounds, the borates. In these compounds, one or more boron atoms are linked to several oxygen atoms to form negatively charged borate ions which, in turn, are associated with positively charged ions, primarily sodium, calcium, or hydrogen (Sprague, 1972). Three common borate salts which are soluble in both water and glycerol are sodium metaborate ($NaBO_2$), sodium perborate ($NaBO_2.H_2O_2.3H_2O$), and sodium pentaborate ($NaB_{10}O_{16}.10H_2O$). The final form of boron in dilute, natural water solutions (undissociated boric acid or negatively charged borate ions) is less dependent on the particular boron compound than on the concentration and/or the acidity or basicity of the solution (Sprague, 1972).

B. Availability to Plants

The average boron concentration in the soil is reported to be about 10 ppm with most soils ranging from 7 to 80 ppm (Krauskopf, 1972). However, higher levels may occur (up to 300 ppm) depending on the origin, climate, rainfall, and other factors (Sprague, 1972). In areas of cultivation, part of the boron content of the surface layers of soil is recycled boron from decayed plant parts (Sprague, 1972). Bradford (1966) has delineated the types of soils in which boron deficiency or excess may occur as follows:

Boron deficiency

- soils naturally low in boron, such as those from igneous rocks
- naturally acid soils, from which boron has been removed by leaching
- light textured, sandy soils
- acid peat and muck soils
- alkaline soils, especially those containing lime
- irrigated soils, where the boron content of the water is low, and where salt or carbonate deposition has occurred
- soils low in organic matter

Boron excess

- soils derived from marine sediments
- arid soils
- soils derived from parent material rich in boron
- soils derived from geologically young deposits

Soils likely to be high in boron, especially arid soils, occur frequently in the Western United States, where irrigation is common. Thus, controlling the boron content of irrigation water may be critical to avoid boron toxicity in sensitive plants (Sprague, 1972). The background level of boron in San Joaquin Valley soils is not available (USBR, 1986)

The total boron content of soil generally is not equivalent to the boron available for uptake by plants. Boron is known to be adsorbed on the surfaces of soil particles; the extent is dependent on the type of soil (with the greatest adsorption associated with fine particles, especially with iron and aluminum compounds on the surface) and pH of the soil (with the greatest adsorption occurring at pH 8.5-9.0) (Sprague, 1972). In most cases, the amount of boron adsorbed at equilibrium is greater than the amount in soil solution, to which plants respond. The adsorbed boron acts as a buffer to maintain more nearly constant concentrations in the soil solution, making correlation of the boron content of irrigation water with the boron content of the soil solution very difficult (Sprague, 1972). The dominant form of inorganic boron in soil solutions is thought to be undissociated boric acid.

Since pKa=9.2 for its first dissociation constant, significant quantities of borate ion will be present only with increasing alkalinity above pH 7 (Loneragan, 1975).

Plants readily take up boron from the soil but the process is influenced by a number of environmental factors, including the pH of the soil solution, temperature, organic matter content, soil texture, soil moisture, and light intensity (Katyal and Randhawa, 1983; Sprague, 1972). The tolerance of plants for boron and the boron requirement for optimal growth vary widely depending upon the species (Eaton, 1944). The mechanism by which boron is taken up and distributed throughout the plant is not well understood. Because the concentration of boron in soil solution is often lower than in the root tissues, active transport against a concentration gradient, as well as simple diffusion, has been proposed to contribute to boron uptake in plants (Sprague, 1972).

Liming may somewhat reduce boron availability in soils (Katyal and Randhawa, 1983), but this decrease is probably related to the need by plant tissues for a specific calcium-boron ratio (National Research Council, 1980). The presence of high calcium or potassium levels in soil can induce boron deficiency in plants; low phosphorus or high nitrate contents can also increase the boron requirements of plants (Sprague, 1972). In culture, choloride ions have been found to enhance boron toxicity during germination of alkali sacaton (a forage grass) (Hyder and Yasmin, 1975).

In addition to being available to terrestrial plants and animals, boron salts in waste water may also exert deleterious effects on the aquatic environment, such as toxicity to fish, water plants, algae, and microorganisms. High doses have been reported to be harmful to the operation of biological waste treatment systems (i.e., activated sludge culture) (Banerji et al., 1968).

C. Mobility

The concentration of boron in plant tissues varies directly with the concentration in soil solution. However, both the boron concentration in leaves and the ratios of leaf to solution concentration were found to vary widely with the type of plant and the concentration in solution (Eaton, 1944). In trace boron solutions, leaf to solution ratios as high as 5000:1 were observed in some plants, and most were in the range of 400 to 1200; in boron solutions ranging from 5 to 25 ppm, ratios were usually less than 200.

Bradford (1966) has used the concentration of boron in plant tissues as a criterion for diagnosis of deficiency or excess of the element in plants. Boron deficiency is seen in a wide variety of plants when vegetative dry matter concentrations are less than 15 ppm. Adequate boron levels range from 20 to 100 ppm in the dry matter. Boron toxicosis in plants occurs when dry tissue concentrations of boron exceed 200 ppm.

Among plants, monocotyledons generally contain less boron than dicotyledons. Berman (1980) has summarized findings on the boron content of plant foods and feeds (edible wet weight basis) as follows: legumes, containing 25-50 ppm, are generally richest in the element; non-leguminous fruits and vegetables contain 5-20 ppm, while cereal grains and hay contain 1-5 ppm; and among fruits, avocados are highest in boron (7-10 ppm).

Boron occurs in much higher concentrations in plant tissues than in animal tissues. Muscle and other soft tissues of the body contain approximately 0.5 to 1.5 ppm boron (dry weight) (Berman, 1980; Underwood, 1977). [Fruits and vegetables generally contain 80-90% water on a fresh weight basis; fresh muscle tissue averages approximately 75% water, see chapters 4, 5, and 6.] Bones concentrate boron and so contain several times the tissue concentration (Berman, 1980; Underwood, 1977). Cow's milk normally contains 0.5-1 ppm boron, but the level depends on the boron intake (Berman, 1980; Underwood, 1977). Dietary boron has been shown to cross the placenta in rats and to increase the boron content in chicken eggs (Hove et al., 1939). Reported intakes of boron by humans are diet dependent, with diets high in fruits and vegetables containing a larger amount than diets high in meat and low in vegetables (Berman, 1980).

IV. ESSENTIALITY/BIOLOGICAL FUNCTION

Boron has long been recognized to be essential to plants (Sprague, 1972; Underwood, 1977). The precise nature of the functioning of boron in plants is unclear. Cell maturation and differentiation in the higher plants seem to be boron dependent (Katyal and Randhawa, 1983). Boron has also been suggested to play a role in the translocation of organic compounds within plants, to influence the activities of plant enzymes, to alter nucleic acid metabolism, and to affect cell wall structure (Jackson and Chapman, 1975; Sprague, 1972).

Several investigators have tried to demonstrate the essentiality of boron for animals (Hove et al., 1939; Orent-Keiles, 1941; Teresi et al., 1944). These workers showed that rats receiving purified diets containing 0.15 to 0.16 ppm boron grew and reproduced as well as rats fed supplemental boron. If boron is an essential element for rats, its requirement must be lower than 0.15 ppm. In rats fed a synthetic diet containing 0.001 ppm boron, hepatic RNA synthesis was stimulated by an intraperitoneal injection of 20 uM boron as boric acid (Weser, 1967), suggesting a possible physiologic function of boron in animals.

V. TOXICOKINETICS

A. Absorption from Gastrointestinal Tract, Lung, Skin

Boron contained in food or administered as soluble borate or boric acid is rapidly and almost completely absorbed from the gastrointestinal tract (Underwood, 1977). Boron in the form of boric acid can be absorbed only slightly through intact skin in rabbits, rats, and humans (Draize and Kelley, 1959; Nielsen, 1970; Pfeiffer et al., 1945); the amounts absorbed in this fashion are apparently too small to induce systemic toxicosis. However, absorption through abraded or burned skin is more efficient and toxic amounts may be absorbed through damaged skin (Draize and Kelley, 1959; Pfeiffer et al., 1945). The absorption of boric acid and borax through the lung is not well studied, but exposure via inhalation has been reported to exert systemic effects (Tarasenko et al., 1972). Exposure via inhalation is an important concern with the boranes (National Research Council, 1980).

B. Distribution

In an attempt to determine the distribution of boric acid in tissues, Pfeiffer et al. (1945) administered 2 g/kg doses to three dogs and measured boric acid content in tissues 24 to 72 hours later. Brain, liver, and adipose tissue, in the order named, were highest in boric acid content.

In nephrectomized mice given large intravenous doses of borax, Locksley and Sweet (1954) observed that, at equilibrium distribution, borate was uniformly distributed throughout the body water, with an excess of 10 to 20% bound in the intracellular compartment. This excess appeared to be more tightly bound in brain than in other tissues.

In young rats (3 weeks old), a single intraperitoneal (i.p.) dose of 42 mg/kg of boron as sodium borate led to a rapid and marked rise (with a maxima achieved within 30 minutes) in the concentration of boron in liver, heart, and blood, but not in brain (Magour et al., 1982). Levels gradually declined to control values within 4 hours. The highest level was seen in the kidney, perhaps because of contamination of this organ with urine. In contrast, the same treatment of older rats (3 months old) resulted in higher concentrations of boron in the liver, heart, and brain than in the blood, indicating the rapid distribution of boron from the blood into these organs. The greatest increase in boron concentration was seen in the kidney. In the more mature rats, maximum concentrations were achieved as rapidly, but were higher and declined more slowly than in younger rats.

In another study, Magour et al. (1982) treated 3-week-old rats with 100 ppm boron (as sodium borate) in the drinking water for 21 days (the daily dose was approximately 20 mg/kg body weight). Boron levels in kidney, liver, and brain increased steadily during the first nine days of treatment and declined thereafter, with concentrations returning to control values in liver and brain. However, the boron levels in blood continued to rise throughout the experimental period. The highest concentration of boron was achieved in kidney.

A study of rats by Hove et al. (1939) indicated that boron, ingested in the form of boric acid, crossed the placenta and was taken up by the fetuses.

In humans, some boron is laid down in the skeleton, but data are minimal (Carson et al., 1986). Stokinger (1981) reported that the mean boron content of 116 ashed samples of autopsied bone from 33 California residents, aged 5 months to 75 years, was 61 ppm bone ash, with a range of 16 to 138 ppm. In other tissues, Hamilton et al. (1972/1973) determined the following boron concentrations, in ug/g wet weight: blood, 0.4; liver, 0.2; kidney, 0.6; muscle, 0.1; lung, 0.6; lymph node, 0.6; brain, 0.06; and testis, 0.09. McNally and Rust (1928) measured boric acid in the tissues of six persons who had died of boric acid poisoning and found the highest concentrations in brain and liver, 0.21 and 0.18%, respectively.

C. Excretion

Urinary excretion is the major route for elimination of boron from the body (Kent and McCance, 1941; Owen, 1944; Tipton et al., 1966). Approximately 80 to 100% of ingested boron may be excreted, unchanged, by this route (Kent and McCance, 1941). Small amounts may be eliminated through the gastrointestinal tract; excretion by other routes is negligible (Carson et al., 1986).

Hove et al. (1939) found that essentially all of a 50 ug oral dose of boron (as boric acid) was excreted by rats in 4 days. In studies of mice given large intravenous doses of borax (18 to 700 ug boron/g body weight), Locksley and Sweet (1954) found that clearance from the blood proceeded with an exponential half-time of approximately 65 minutes.

VI. TOXICITY

A. Animals

Studies designed to determine the mean lethal dose and toxic effects of boron compounds have been conducted in a variety of species with various routes of administration. The toxicity of borax and boric acid has been evaluated by the Select Committee on GRAS Substances (1980). In the following discussion, more emphasis is placed on results obtained with ingestion, inhalation, and dermal exposure than with routes of administration involving injection (i.e., subcutaneous, intraperitoneal, and intravenous).

1. Acute/short-term exposures

Pfeiffer et al. (1945) determined the oral LD_{50} for boric acid to be 3.45 g/kg in mice and 2.66 g/kg in rats. The toxicity of boric acid was enhanced by subcutaneous and intravenous administration. These investigators also tested the acute toxicity of boric acid in dogs by administering single oral doses of 0.2, 0.4, 0.8, 1.0, 1.5, and 2.0 g/kg to animals previously given an antiemetic injection of morphine. Half of the dogs treated with 2.0 g/kg boric acid died, and the authors suggested that this dose approximated the median lethal oral dose. Signs of intoxication were observed in most of the dogs given the two highest doses. These included cyanosis of mucous membranes, rigidity of the limbs, and convulsions.

Verbitskaya (1975) reported the acute oral LD_{50} for boron in the form of boric acid and borax to be approximately 300 mg/kg for rabbits, guinea pigs, and dogs, and to range from 470 to 700 mg/kg for mice and rats. They did not detect sex differences in sensitivity to boron.

Weir and Fisher (1972) studied the acute oral toxicity of borax and boric acid in rats and dogs. In male Sprague-Dawley rats, the LD_{50} was 4.50 g/kg for borax and 3.45 g/kg for boric acid (0.51 and 0.60 g/kg boron, respectively); in females of the same strain the LD_{50} was 4.98 g/kg for borax and 4.08 g/kg for boric acid (0.56 and 0.71 g/kg boron, respectively). The LD_{50} in male Long-Evans rats was determined to be 6.08 g/kg for borax and 3.16 g/kg for boric acid (0.69 and 0.55 g/kg boron, respectively). The signs of toxicity were similar for the two boron compounds and included depression, ataxia, and convulsions before death. In dogs, the acute per os (oral) administration of borax at doses ranging from 1.54 to 6.51 g/kg and boric acid at doses ranging from 1.0 to 3.98 g/kg resulted in vomiting within the first hour by almost all animals, except for a few at the lowest dose. The severity of this response varied with the dose. None of the treated dogs died during the 14-day period following administration of the boron compounds.

The acute per os LD_{50} for borax in rats was found to be 3.48 g/kg (396 mg/kg boron) by Wang (1984). Boron poisoning was reported to have deleterious effects on the central nervous system, the digestive tract, and the skin.

Draize and Kelley (1959) administered four daily oral doses of aqueous solutions of boric acid to rabbits at doses ranging from 100 to 1000 mg/kg. Under these conditions, the LD_{100} for boric acid was 850 mg/kg. Four daily oral doses of 800 mg/kg caused no deaths, but produced severe symptoms of toxicity including anorexia, weight loss, and diarrhea. At dose levels of 600 and 700 mg/kg, minor signs of toxicity were noted.

Other investigations of the effects of boron compounds have been conducted for durations of up to six months. One of the earliest of these was the study reported by Pfeiffer et al. (1945) in which five groups of 20-24 "immature" rats were given various levels of boric acid in drinking water. Concentrations of 0.25% and higher produced growth inhibition after 20 to 30 days, but did not produce changes in blood counts or evidence of gross or microscopic pathologic lesions.

Three-month-old male rats, five per group, were given daily per os doses of aqueous solutions of borax or boric acid (1 g/kg body weight) for 3 weeks by Dani et al. (1971). Treatment with both boron compounds led to growth depression. The RNA content (ug/mg of wet tissue) of liver, brain, and kidney was higher in animals treated with boric acid and borax than in control animals. The DNA content was similarly elevated in the brain and kidney of both treated groups, but the DNA content of liver was decreased 50% by administration of boron. Protein and nitrogen contents of brain, liver, and kidney were elevated in some cases and decreased in others.

Stimulation of RNA synthesis by boric acid in livers of male rats was determined by measurement of 6-^{14}C-labeled orotic acid incorporation into RNA (Weser, 1967). Liver RNA synthesis was markedly increased by intraperitoneal injection of boric acid, whereas stimulation was less marked when rats were fed a diet containing 1 ppm boron (as boric acid) for 6 weeks. DNA synthesis, measured by incorporation of 6-^{3}H-thymidine, was not affected by either route of boric acid administration.

Weir and Fisher (1972) studied the effects of various dietary levels of boric acid and borax in young Sprague-Dawley rats (81-119 g) for 90 days (10 males and 10 females per group). Dietary concentrations fed were 52.5, 175, 525, 1750, and 5250 ppm boron, added to a commercial ration. Rats fed 1750 and 5250 ppm of boron as borax or boric acid had a rapid respiration, inflamed eyes, swollen paws, and desquamated skin on the paws and tails, and the males had atrophied scrotums during the last weeks of the study. The appearance of animals consuming lower levels of boron was comparable to that of controls. At 5250 ppm boron, both borax and boric acid resulted in the deaths of all animals within 3 to 6 weeks. Growth and feed efficiency were significantly reduced for males fed borax at 1750 ppm boron and for both males and females at 5250 ppm boron. At the 1750 ppm boron level, boric acid reduced growth and food consumption in both males and females. Organ to brain weight ratios (taken as an index of organ damage) were not affected in rats fed 525 ppm boron or less. However, the organ/brain weight ratios decreased uniformly in both males and females fed 1750 ppm boron as either borax or boric acid. Complete testicular atrophy was detected in all males fed 1750 ppm boron as either borax or boric acid, and partial atrophy was seen in four males fed 525 ppm as borax and in one male fed 525 ppm as boric acid. Necropsies of the animals that died showed congestion of liver and kidneys, bright red lungs, and in several animals a swollen brain, small gonads, and a thickened pancreas.

Weir and Fisher (1972) also fed diets containing borax or boric acid (17.5, 175, or 1750 ppm boron) to male and female beagle dogs (five per group) for 90 days. With one exception (a male that died of diarrhea) all dogs were essentially normal in appearance, behavior, elimination, body weight, and food consumption. Hematologic, biochemical, and urine values were within normal limits, except for decreased hemoglobin and packed cell volume in five animals fed the highest level of borax (1750 ppm boron). Increases in brain/body weight ratio and liver/body weight ratio occurred in dogs fed borax and boric acid, respectively, at the 1750 ppm boron level. At the same level, both borax and boric acid caused significant decreases in thyroid and testes/body weight ratios. No histologic alterations were seen in animals fed 175 ppm boron or less. Both borax and boric acid at the 1750 ppm level produced severe testicular atrophy, with degeneration of the spermatogenic epithelium, in all male dogs. Evidence of red blood cell destruction (hemosiderin in reticular cells of liver and spleen and in the proximal tubules of the kidney) was somewhat greater in the dogs fed borax than in those fed boric acid.

Dixon et al. (1976) evaluated the effects of boron on the reproductive system of male rats. In subchronic studies, treatment groups were allowed free access to drinking water containing borax, at boron concentrations of 0.3, 1.0, or 6.0 mg/L for periods up to 90 days. Plasma levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were not altered by consumption of borax. This study also failed to reveal any reproductive effects or biologically significant change in clinical serum chemistry or weight of the body, testis, prostate, or seminal vesicles. Fructose and zinc levels and acid phosphatase activity were unaltered by the levels of boron used in this study. Forced breeding studies did not reveal any effects of boron treatment on male fertility.

Seal and Weeth (1980) studied the effects of boron in drinking water on weanling Long-Evans hooded male rats. Fifteen animals per treatment were offered deionized drinking water, ad lib, to which 0, 150, and 300 mg boron per liter were added as borax for 70 days. The rats consumed a commercial laboratory ration which contained 54 ppm boron. Rats that consumed drinking water containing 150 and 300 ppm boron had body weights 7.8 and 19.8% less than the control group. No differences among treatment were observed in the mean covariance-adjusted weights of kidneys, liver, or adrenals. The testes, seminal vesicle, spleen, and right femur weights were significantly lower with boron-containing water. At the highest level, boron supplementation also interfered with spermatogenesis. Plasma triglyceride concentrations were depressed in both boron-treated groups. In the rats consuming 300 ppm boron in water, plasma alkaline phosphatase activity, total protein level, osmotic pressure, and hematocrit were all reduced.

The responses of heifers to tap water alone (0.8 ppm boron) or containing 150 or 300 ppm boron added as boric acid were studied by Green and Weeth (1977). Twelve Hereford heifers were used in a 3x3 latin-square design with four squares, for periods of 30 days. The hay consumed by the animals contained 38.3 ppm boron. At 150 and 300 ppm boron in drinking water, hay consumption decreased and weight loss was noted. Both levels of boron supplementation produced a significant decrease in hematocrit and in plasma phosphate. The plasma boron concentrations were 0.53, 11.2, and 18.9 mg/L in animals consuming 0, 150, and 300 ppm added boron, respectively. Urinary excretion accounted for 30, 67, and 69% of the total daily boron intake on the three respective treatments. Urinary excretion of phosphorus was also increased by consumption of added boron.

2. Chronic exposure

Weir and Fisher (1972) conducted chronic oral toxicity trials of borax and boric acid in rats. The control group of 70 male and 70 female weanling Sprague-Dawley rats received the basal diet. The test groups of 35 males and 35 females each received the basal diet with added borax or boric acid at 117, 350, and 1170 ppm boron for 2 years. The appearance and behavior of rats fed borax and boric acid at 117 and 350 ppm boron did not differ from controls, nor did hematologic variables and organ histology. The following signs of toxicity were observed among rats fed the highest concentration of boron compounds (1170 ppm boron): coarse hair, scaly tails, hunched position, swelling and desquamation of the pads of the paws, abnormally long toenails, shrunken scrotums, inflamed eyelids, and bloody discharge from the eyes. At 1170 ppm boron, both compounds resulted in decreased food consumption and suppressed growth; borax resulted in low packed cell volumes in males and females and boric acid resulted in low values in females. Atrophic testes were found in male rats fed either borax or boric acid at 1170 ppm boron equivalent at 6, 12, and 24 months. The testes weights and testes/body weights were significantly lower, whereas the brain and thyroid/body weight ratios were significantly higher than in controls.

Weir and Fisher (1972) also examined the oral toxicity of borax and boric acid in a chronic study of dogs. The control group of four male and four female young beagles received the basal diet. The test groups of four male and four female dogs received the diet with borax or boric acid added at levels of 58, 117, 350 ppm boron equivalent for 2 years. An additional test group received borax and boric acid in the diet at 1170 ppm boron for 38 weeks. At 58, 117, and 350 ppm boron, neither borax nor boric acid had appreciable effects on appearance, behavior, food consumption, body weight, organ weights, or organ/body weight ratios. Borax-fed dogs had hematologic and biochemical values within normal limits. Ingestion of borax and boric acid at 1170 ppm boron did not produce any adverse effects except testicular degeneration.

Random-bred white male rats were given boric acid in drinking water at boron concentrations of 0, 0.3, 1.0, and 6.0 mg/L (0, 0.015, 0.05, and 0.3 mg/kg body weight, respectively) for 6 months (Krasovskii et al., 1976). Boron consumption in 0.3 mg/kg doses produced increased blood aldolase levels, reduction in the relative weight of the gonads, decreased spermatozoa mobility, and other manifestations of a gonadotropic effect. At the two highest boron concentrations, a decrease in the lactic acid content of liver and a tendency towards a drop in liver glycogen were observed.

In a life-time study of random-bred white Swiss male and female mice (Charles River CD strain) given drinking water containing 5 ppm of boron as sodium metaborate, Schroeder and Mitchener (1975) found no differences in growth, mortality, or survival between boron treated and control animals.

B. Human

1. Acute/short-term exposures

A plethora of reports have appeared in the literature describing fatal and nonfatal poisonings with boric acid and other boron compounds, with a large number of these cases occurring in children. A frequent source of boric acid in fatal poisoning in infants has been baby powder containing this ingredient (as an antiseptic), applied to denuded skin (Abramson, 1949; Brooke, 1954; Fellows et al., 1948; Hallett, 1955; Rosen and Haggerty, 1956; Skipworth et al., 1967; Valdes-Dapena and Arey, 1962; Watson, 1945). Other routes of exposure for children have been accidental substitution of boric acid for ingredients in infant formula (Rubenstein and Musher, 1970) and feeding mixtures of honey and borax (Gordon et al., 1973). In adults, short-term treatment of burns with boric acid ointment (Baker and Wilson, 1963; Pfeiffer et al., 1945) and accidental ingestion of boric acid have been common sources of poisoning.

Signs and symptoms arising from the ingestion or dermal absorption of boric acid include nausea, vomiting, diarrhea, abdominal cramps, and erythematous lesions on skin and mucous membranes. With higher doses circulatory collapse, tachycardia, cyanosis, delirium, convulsions, and coma may occur (Stokinger, 1981; Valdes-Dapena and Arey, 1962). The lowest oral lethal dose for humans has been reported to be 640 mg/kg, and the lowest lethal dose by the skin, 8600 mg/kg (Stokinger, 1981).

Fisher (1951) and Valdes-Dapena and Arey (1962) reported intracytoplasmic inclusions in the pancreas of infants who died of boric acid poisoning. However, Sanusi et al. (1975) have questioned the value of this finding as a diagnostic lesion.

Experience with the rapid administration of large intravenous doses of borax has been obtained with patients undergoing neutron capture therapy for brain tumors. Locksley and Farr (1955) studied ten patients who received one to four injections of 14 to 20 g borax (1.5 to 2.0 g boron), at intervals of 2 weeks to 3 months. Within 2 minutes after administration, nausea and emesis occurred, and urgent defecation and micturition frequently were experienced. Abnormalities in electrocardiograms that persisted for several days were also observed in seven patients given 19 to 27 g borax (32 to 50 mg boron/kg body weight) by Conn et al. (1955).

2. Chronic exposure

Very few studies of toxicity due to chronic exposure to boron compounds have been conducted. Tarasenko (1972) used a questionnaire to assess sexual function in 30 to 40-year-old men who had experienced 10 or more years of industrial exposure (mainly via inhalation) to boric acid. Compared to a control group of the same age without exposure to boric acid, the exposed workers reported "lowering of sexual activity and a general level of sexual disruption." Despite some differences in the number and function of spermatozoa, the number of pregnancies among the wives of the workers did not differ from the wives of the control subjects.

Krasovskii et al. (1976) compared sexual function (by means of a questionnaire) in two groups of men exposed to differing concentrations of boron in drinking water and reported a reduction in function in those exposed to a level of 0.3 mg/kg boron compared to a control group.

Two cases of toxic alopecia resulting from chronic exposure to boron compounds have been reported. One occurred in a subject exposed (via inhalation and dermal contact) nearly daily for 6 years to a washing powder containing borax (Tan, 1970). The other case involved a subject who had chronically ingested large quantities of mouthwashes containing boric acid (Stein et al., 1973).

C. Mutagenicity

Demerec et al. (1951) showed that boric acid, at concentrations of 1.8 to 4.0%, was capable of inducing back-mutations in Sd-4 (streptomycin-dependent) *Escherichia coli*. Using two modifications of this procedure, Iyer and Szybalski (1958), however, failed to demonstrate any mutagenic activity for boric acid.

D. Carcinogenicity

An increase in tumor production was not seen in a life-time study of random-bred white Swiss male and female mice (Charles River CD strain) given drinking water containing 5 ppm of boron as sodium metaborate (Schroeder and Mitchener, 1975).

E. Reproductive Toxicity

Tarasenko et al. (1972) studied the effects of inhalation of boric acid aerosol on the reproductive function of male rats. Two test groups of 12 animals each were exposed to boric acid aerosol at concentrations of 9.6 ± 0.5 mg/m^3 or 48.6 ± 1.46 mg/m^3 for daily 4-hour periods of exposure over the course of 4 months. Following the exposure, six animals from each of the test groups and the control group were mated with healthy females. A complete loss of male fertility was observed in both test groups, as evidenced by failure to detect any spermatozoa in vaginal smears. Boric acid aerosol at the lower concentration caused testicular atrophy and markedly reduced spermatozoa number and mobility. At the higher concentration, male rats produced only isolated spermatozoa. Animals exposed to the higher concentration of boric acid aerosol also showed a persistent reduction in body weight.

The reproductive performance of male rats fed borax in diets containing 500, 1000, or 2000 ppm boron was studied by Lee et al. (1978) and Dixon et al. (1979) for periods of 30 or 60 days. Adverse effects were not observed with 500 ppm boron. Animals fed diets containing 1000 or 2000 ppm boron had fewer germinal cells and decreased diameters of seminiferous tubules, but most of the Leydig and Sertoli cells appeared normal. The testicular atrophy was associated with decreases in the specific activities of testicular hyaluronidase, dehydrogenases of sorbitol, and lactate dehydrogenase isoenzyme-X. Plasma testosterone levels were unchanged, but plasma FSH and LH levels were increased. The observed abnormalities were more severe as the level of boron consumed and the period of exposure increased. Males consuming 1000 ppm boron for 30 and 60 days had markedly reduced fertility rates for 3 and 4 weeks, respectively, after termination of boron treatment. Consumption of 2000 ppm boron for 30 days led to significantly reduced fertility for 8 weeks; infertility was only partially reversed thereafter. Consumption of the same diet for 60 days produced complete infertility which was not reversed for at least 32 weeks after the cessation of boron treatment. Mating behavior was normal. When pregnancy occurred, boron treatment did not affect litter size. These results suggested that boron-induced infertility was caused by germinal aplasia rather than a dominant lethal effect. Testicular concentrations of 6 to 8 ppm boron appeared to be toxic to spermatogenic cells.

Many studies of the teratogenic effects of boric acid on the chick embryo have been conducted, although their relevance to mammalian systems is not known (Select Committee on GRAS Substances, 1980). Landauer (1952, 1954) injected 2.5 mg of boric acid into yolk sacs of chick embryos 24 hours after fertilization or 1.0, 2.5, or 2.5 mg boric acid at 96 hours. Injection of boric acid at 24 hours of incubation gave rise to rumplessness; injection at 96 hours caused decreased body size, shortening of the lower beak, facial coloboma, and cleft palate in 13-day embryos. The incidence of abnormalities and mortality increased with increasing dose of boric acid. Hatched chicks that had been treated with boric acid at 96 hours incubation frequently displayed "curled toe paralysis," a disorder associated with inadequate riboflavin during embryonic development. Administration of riboflavin with boric acid reduced the incidence of abnormalities in chick embryos (Landauer and Clark, 1964). Simultaneous administration of substances that form complexes with boric acid (D-ribose, D-sorbitol hydrate, or pyridoxine hydrochloride) also reduced mortality and the incidence of abnormalities in chick embryos treated with boric acid (Landauer, 1953).

Goldie and Stierholz (1964) found that treatment with 2.5 mg of boric acid at 24 hours affected the development of neural tube, notocord, and tailgut in 3-day embryos. The same histological effects were also seen with smaller doses (200 ug) given at 28 hours. Other adverse effects of boric acid detected in chick embryos included delayed erythrocyte maturation (Sherman and Fox, 1955), depressed hemoglobin and hematocrit values (Rosky et al., 1957), and paleness, edema, and retardation of feather growth (Ridgway and Karnofsky, 1952). The latter investigators also determined the LD_{50} for boric acid administered by the yolk sac route to be 5 mg/egg at 4 days and 7 mg/egg at 8 days incubation. By the chorioallantoic membrane route, the LD_{50} was 5 mg/egg at 8 days incubation.

In a three-generation reproduction study of rats, Weir and Fisher (1972) found that borax or boric acid fed in the diet at levels of 117 or 350 ppm boron did not produce adverse effects on litter size, live births, or weight of progeny and did not cause gross abnormalities in organs. Consumption of a higher level of the two compounds (1170 ppm boron equivalent) rendered the animals sterile.

F. Mechanism of Toxicity

The mechanism of toxicity of boron has not been clearly established. Boric acid can form complexes with compounds such as glucose, riboflavin, and ascorbic acid (Zittle, 1951), and borate can react with the ribose moiety of nicotinamide adenine dinucleotide (NAD) and nicotinamide mononucleotide (NMN) (Johnson and Smith, 1976). Weser (1966) showed that excess borate at pH 7.0-8.5 could react with epinephrine and inhibit the epinephrine-induced activation of dephosphorylase in perfused liver of dogs. Roe et al. (1972) has suggested that one of the mechanisms of toxicity of boron may be the formation of complexes with riboflavin. They found that the growth depression induced by a riboflavin-deficient diet in rats and guinea pigs was exacerbated by the inclusion of 1% boric acid in the diet, and that dietary boric acid increased the excretion of riboflavin in rats. Pinto et al. (1978) found a relatively high level of riboflavin in the urine of persons who had accidentally or purposely ingested boric acid or commercial borax products.

In vitro, boric acid and borates have been observed to inhibit the activity of a wide variety of enzymes, including riboflavin-dependent xanthine oxidase (Roush and Norris, 1950), glucose-6-phosphatase and phosphohexose isomerase (Ganguli et al., 1963), glyceraldehyde phosphate dehydrogenase (Kaneshima et al., 1968; Misawa et al., 1966), and alkaline phosphatase (Zittle and Della Monica, 1950).

G. Interactions with Other Substances Affecting Toxicity

The effect of glucose on borate toxicity has been investigated. Easterday and Farr (1961) gave mice intravenous doses of a normally toxic amount of borax with varied concentrations of glucose and found that increased glucose diminished the toxicity of borax. Glucose also decreased the toxicity of sodium pentaborate and sodium tetraborate administered intravenously or intraperitoneally (Easterday and Hamel, 1963).

Administration of excess riboflavin to chicks fed boric acid mitigated the signs of boron toxicity (Roe et al., 1972).

VII. TREATMENT

Removal from exposure is an important element of treatment for boron intoxication. A specific antidote for poisoning by the common boron compounds found in nature has not been identified. In cases of acute poisoning, efforts should be directed toward combating shock and promoting the excretion of boron.

VIII. TYPICAL EXPOSURE LIMITS/BODY BURDEN/TOXIC LIMITS

As an essential nutrient for plants boron is ubiquitous and, thus, is widely distributed in foods. Average drinking water concentrations are reported to be 0.114 ppm (Carson et al., 1986). A representative U.S. diet for adults providing 4200 kcal was calculated to contain approximately 3 mg of boron per day (Zook and Lehmann, 1965), although estimated boron intakes of adult humans around the world were reported to vary from 0.3 to 41.0 mg due to geographic differences (Schlettwein-Gsell and Mommsen-Straub, 1973). Other estimates of daily boron intake range from 10 to 20 mg/day (Kent and McCance, 1941).

The body burden of a 70-kg reference man is estimated to be 200 mg boron with 140 mg in soft tissues (Snyder et al., 1975). Boron is distributed throughout the tissues and organs at concentrations mostly between 0.5 and 1.0 ppm dry basis in the soft tissues and several times these levels in the bone (Underwood, 1977).

Safe levels for dietary intake of boron by humans have not been recommended. The National Research Council (1980) reported that the U.S. Department of Interior in 1971 established an upper limit of 1 ppm for boron in public water supplies and that the Environmental Protection Agency in 1973 proposed 5 ppm boron as the allowable maximum in water for livestock. The National Research Council (1980) also suggested that 150 ppm boron in the dry diet of cattle was the maximum tolerable level, and one which might be extrapolated to other species. Sittig (1985) reported that the Environmental Protection Agency in 1976 established a criterion for boron of 750 ppb for long-term irrigation of sensitive crops and more recently suggested an ambient water limit of 43 ppb (USEPA, 1977). Gosselin et al. (1985) noted that a lethal dose of boric acid for humans might be less than 1 g/kg. Sax (1984) reported the fatal dose of orally ingested boric acid to be 15 to 20 g for adults and 5 to 6 g for infants, i.e., 200 mg/kg.

IX. INDICATORS OF EXCESSIVE ACCUMULATION

A. Index

Little attention has been given to developing an index to monitor boron accumulation. However, with excess ingestion or absorption of boron, circulating levels and excretion through the kidneys are known to increase. Therefore, blood and urine would seem to be useful samples to assay to assess boron status. The study of Weeth et al. (1981) indicated that the boron status of cattle could be predicted from the boron content of plasma and urine.

B. Method

Berman (1980) has reviewed methods for the determination of boron. Tumeric yellow or curcumin is the classical reagent for the colorimetric detection of boron. This qualitative method was adapted for spectrophotometric determination of boron extracted from animal tissue by Mair and Day (1972) and permitted detection of boron in the range 2 to 20 ng/ml. Boric acid forms fluorescent compounds with various reagents, and this property has been used as the basis for several boron assays. Boron in water has been measured by proton activation analysis (Bankert et al., 1973) and atomic emission spectroscopy (Pierce and Brown, 1976). Stokinger (1981) recommended a spectrographic procedure for the determination of boron in biological samples.

C. Basis for Interpretative Criteria

Standards for the interpretation of blood and urine levels of boron have not been established. Stokinger (1981) has reported the median boron concentration in blood to be 9.76 ug/100 ml, with a range of 3.90 to 36.50, and the median concentration in urine to be 720 ug/L, with a range of 40 to 6600. These values were derived from a study of 300 men employed in various industries throughout the continental United States. In one subject who experienced toxicity caused by chronic ingestion of excess boric acid, the blood boron level was found to be 0.3 mg/100 ml (Stein et al., 1973). However, in two children who drank a large quantity of boric acid without evidence of toxicity, blood levels of 7.44 and 7.89 mg/100 ml were reported (Fisher and Freimuth, 1958).

D. Quality Control/Quality Assurance

In addition to the precautions required for the appropriate analysis of all trace elements, a special concern in the analysis of boron is the need to avoid contact of the samples with borosilicate glass. Green et al. (1976) have shown that although water solutions did not seem to extract boron from the glass, solutions of 0.1M hydrochloric acid and 0.1M sodium hydroxide extracted 0.03 and 0.08 ug/ml of boron, respectively, within 24 hours. A solution of 1M sodium hydroxide extracted 0.03 ug/ml within 5 minutes.

X. SPECIAL CONSIDERATIONS

Recent studies have indicated that boron can affect major mineral metabolism and that boron might be an important nutritional determinant of the incidence of osteoporosis. Nielsen et al. (1987) conducted a metabolic ward study of dietary boron in 12 postmenopausal women aged 48 to 82 years. The women consumed a diet of ordinary foods with a low boron content (0.25 mg/d) for 119 days. Thereafter, the women participated in two additional 24-day dietary periods during which the basal diet was supplemented with boron (3 mg/d) as sodium borate, in divided doses with meals. The consumption of magnesium and aluminum was also varied. Boron supplementation markedly reduced the urinary excretion of calcium and magnesium; this effect was more pronounced when the women were consuming the low-magnesium diet than the adequate-magnesium diet. The urinary excretion of phosphorus was depressed by boron supplementation when the women consumed the low-magnesium, but not the adequate-magnesium, diet. Boron supplementation also produced significant elevations in the serum concentrations of 17ß-estradiol and testosterone, greater increases were observed when dietary magnesium was low. Supplemental aluminum did not affect the variables tested. The results suggested that the effects of boron on mineral metabolism were mediated through some endocrine or biochemical mechanism, rather than through chemical or complexing effects of boron. These findings need further investigation, but suggest that supplementation with boron in amounts contained in diets high in fruits and vegetables can cause changes in the mineral metabolism of postmenopausal women consistent with the prevention of calcium loss and bone demineralization.

REFERENCES

Abramson, H. 1949. Fatal boric acid poisoning in a newborn infant. Pediatrics 4:719-722.

Baker, D.H.; Wilson, R.E. 1963. The lethality of boric acid in the treatment of burns. J. Am. Med. Assoc. 186:1169-1170.

Banerji, S.K.; Bracken, B.D.; Garg, B.M. 1968. Effect of boron on aerobic biological waste treatment. Eng. Bull. Purdue Univ., Eng. Ext. Serv. 132(Pt. 2):956-965.

Bankert, S.F.; Bloom, S.D.; Sauter, G.D. 1973. Trace element analysis in water by proton activation. Anal. Chem. 45:692-697.

Berman, E. 1980. Toxic metals and their analysis. London: Heyden & Son Ltd. p.59-64.

Bradford, G.R. 1966. Boron. In: Chapman, H.D., ed. Diagnostic criteria for plants and soils. Berkeley: University of California. p.33-61.

Brooke, C.E. 1954. The boric acid problem. Excerpta Med. 8:238-241.

Carson, B.L.; Ellis, H.V., III; McCann, J.L. 1986. Toxicology and biological monitoring of metals in humans including feasibility and need. Chelsea, MI: Lewis Publishers, Inc. p.48-50.

Conn, H.L., Jr.; Antal, B.B.; Farr, L.E. 1955. The effect of large intravenous doses of sodium borate on the human myocardium as reflected in the electrocardiogram. Circulation 12:1043-1046.

Dani, H.M.; Saini, H.S.; Allag, I.S.; Singh, B.; Sareen, K. 1971. Effect of boron toxicity on protein and nucleic acid contents of rat tissues. Res. Bull. Punjab Univ. 22(Parts 1-2):229-235.

Demerec, M.; Bertani, G.; Flint, J. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Nat. 85:119-135.

Dixon, R.L.; Lee. I.P.; Sherins, R.J. 1976. Methods to assess reproductive effects of environmental chemicals: studies of cadmium and boron administered orally. Environ. Health Perspect. 13:59-67.

Dixon, R.L.; Sherins, R.J.; Lee. I.P. 1979. Assessment of environmental factors affecting male fertility. Environ. Health Perspect. 30:53-68.

Draize, J.H.; Kelley, E.A. 1959. The urinary excretion of boric acid preparations following oral administration and topical applications to intact and damaged skin of rabbits. Toxicol. Appl. Pharmacol. 1:267-276.

Easterday, O.D.; Farr. L.E. 1961. Alteration of borate toxicity by D-glucose. J. Pharmacol. Exp. Ther. 132:392-398.

Easterday, O.D.; Hamel, H. 1963. Acute intravenous and intraperitoneal toxicity studies on sodium pentaborate decahydrate and sodium tetraborate decahydrate. Arch. Intern. Pharmacodyn. Ther. 143:144-164.

Eaton, F.M. 1944. Deficiency, toxicity, and accumulation of boron in plants. J. Agr. Res. 69:237-277.

Fellows, A.W.; Campbell, J.S.; Wadsworth, R.C. 1948. Boric acid--poison. J. Maine Med. Assoc. 39:339-344.

Fisher, R.S. 1951. Intracytoplasmic inclusions in the pancreas due to boric acid poisoning. Am. J. Pathol. 27:745 (Abstract).

Fisher, R.S.; Freimuth, H.C. 1958. Blood boron levels in human infants. J. Invest. Dermatol. 30:85-86.

Ganguli, N.C.; Arora, B.S.; Bhalerao, V.R. 1963. Inhibition of certain glycolytic enzymes of rat tissues by boric acid. Indian J. Exp. Biol. 1:228-229.

Goldie, M.; Stierholz, H. 1964. Histologic features of the development of the rumpless chick embryo induced with boric acid. J. Am. Osteopath. Assoc. 63:879-880.

Gordon, A.S.; Prichard, J.S.; Freedman, M.H. 1973. Seizure disorders and anemia associated with chronic borax intoxication. Can. Med. Assoc. J. 108:719-721,724.

Gosselin, R.E.; Smith, R.P.; Hodge, H.C. 1985. Clinical toxicology of commercial products. 5th Edition. Baltimore: Williams & Wilkins. p.II-118.

Green, G.H.; Blincoe, C.; Weeth, H.J. 1976. Boron contamination from borosilicate glass. J. Agr. Food Chem. 24:1245-1246.

Green, G.H.; Weeth, H.J. 1977. Responses of heifers ingesting boron in water. J. Anim. Sci. 46:812-818.

Hallett, G.W., Jr. 1955. Boric acid poisoning: case report. J. Maine Med. Assoc. 46:93.

Hamilton, E.I.; Minski, M.J.; Cleary, J.J. 1972/1973. The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom: an environmental study. Sci.Total Environ. 1:341-374.

Hansen, S.R.; Morehardt, J.E. 1987. Identification of potential substances-of-concern in agricultural drainage waters from the San Joaquin Valley: a screening level analysis. Prepared for the San Joaquin Valley Drainage Program, Sacramento, CA under EA Prop BAC 72A by E.A. Engineering, Science, and Technology, Inc., Lafayette, CA.

Hove, E.; Elvehjem, C.A.; Hart, E.B. 1939. Boron in animal nutrition. Am. J. Physiol. 127:689-701.

Hyder, S.Z.; Yasmin, S. 1975. Boron tolerance and enhancement of boron toxicity by chloride ions in alkali sacaton during germination of Sporobolus airoides Torr. Experientia 31:427-428.

Iyer, V.N.; Szybalski, W. 1958. Two simple methods for the detection of chemical mutagens. Appl. Microbiol. 6:23-29.

Jackson, J.F.; Chapman, K.S.R. 1975. The role of boron in plants. In: Nicholas, D.J.D.; Egan, A.R., eds. Trace elements in soil-plant-animal systems. New York: Academic Press, Inc. p.213-225.

Johnson, S.L.; Smith, K.W. 1976. The interaction of borate and sulfite with pyridine nucleotides. Biochemistry 15:553-559.

Kaneshima, H.; Kitsutaka, T.; Akagi, M. 1968. Studies on the metabolic effects of borate. VI. Effects of borate on the reduction of methemoglobin. Chem. Pharm. Bull. (Tokyo) 16:246-250.

Katyal, J.C.; Randhawa, N.S. 1983. Micronutrients. FAO Fertilizer and Plant Nutrition Bulletin 7. Rome: Food and Agriculture Organization of the United Nations. p.57-67.

Kent, N.L.; McCance, R.A. 1941. The absorption and excretion of 'minor' elements by man. I. Sliver, gold, lithium, boron and vanadium. Biochem. J. 35:837-844.

Krauskopf, K.B. 1972. Geochemistry of micronutrients. In: Mortvedt, J.J.; Giordano, P.M.; Lindsay, W.L., eds. Micronutrients in agriculture. Madison, WI: Soil Science Society of America, Inc.

Krasovskii, G.N.; Varshavskaya, S.P.; Borisov, A.I. 1976. Toxic and gonadotropic effects of cadmium and boron relative to standards for these substances in drinking water. Environ. Health Perspect. 13:69-75.

Landauer, W. 1952. Malformations of chicken embryos produced by boric acid and the probable role of riboflavin in their origin. J. Exp. Zool. 120:469--508.

Landauer, W. 1953. Complex formation and chemical specificity of boric acid in production of chicken embryo malformations. J. Cell. Comp. Physiol 43(Suppl. 1):261-305.

Landauer, W. 1954. On the chemical production of developmental abnormalities and of phenocopies in chicken embryos. Proc. Soc. Exp. Biol. Med. 82:633-636.

Landauer, W.; Clark, E.M. 1964. On the role of riboflavin in the teratogenic activity of boric acid. J. Exp. Zool. 156:307-312.

Lee, I.P.; Sherins, R.J.; Dixon, R.L. 1978. Evidence for induction of germinal aplasia in male rats by environmental exposure to boron. Toxicol. Appl. Pharmacol. 45:577-590.

Locksley, H.B.; Farr, L.E. 1955. The tolerance of large doses of sodium borate intravenously by patients receiving neutron capture therapy. J. Pharmacol. Exp. Ther. 114:484-489.

Locksley, H.B.; Sweet, W.H. 1954. Tissue distribution of boron compounds in relation to neutron-capture therapy of cancer. Proc. Soc. Exp. Biol. Med. 86:56-63.

Loneragan, J.F. 1975. The availability and absorption of trace elements in soil-plant systems and their relation to movement and concentration of trace elements in plants. In: Nicholas, D.J.D.; Egan, A.R., eds. Trace elements in soil-plant-animal systems. New York: Academic Press, Inc. pp.109-134.

Magour, S.; Schramel, P.; Ovcar, J.; Maser, H. 1982. Uptake and distribution of boron in rats: interaction with ethanol and hexobarbital in the brain. Arch. Environ. Contam. Toxicol. 11:521-525.

Mair, J.W., Jr.; Day, H.G. 1972. Curcumin method for spectrophotometric determination of boron extracted from radiofrequency ashed animal tissues using 2-ethyl-1,3-hexanediol. Anal. Chem. 44:2015-2017.

McNally, W.D.; Rust, C.A. 1928. The distribution of boric acid in human organs in six deaths due to boric acid poisoning. J. Am. Med. Assoc. 90:382-383.

Misawa, T.; Kaneshima, H.; Akagi, M. 1966. Studies on the metabolism of borate. IV. Effect of borate on glyceraldehydephosphate dehydrogenase. Chem. Pharm. Bull. (Tokyo) 14:467-473.

National Research Council, Subcommittee on Mineral Toxicity in Animals. 1980. Nutrients and toxic substances in water for domestic animals. Washington, DC: National Academy of Sciences Press. p.71-83.

Nielsen, F.H.; Hunt, C.D.; Mullen, L.M.; Hunt, J.R. 1987. Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women. FASEB J. 1:394-397.

Nielsen, G.H. 1970. Percutaneous absorption of boric acid from boron-containing preparations in rats. Acta Pharmacol. Toxicol. 28:413-424.

Norrish, K. 1975. Geochemistry and mineralogy of trace elements. In: Nicholas, D.J.D.; Egan, A.R., eds. Trace elements in soil-plant-animal systems. New York: Academic Press, Inc. pp.55-81.

Office of the Federal Register, General Services Administration. 1980. Code of Federal Regulations. Title 21: food and drugs, parts 170-199 rev. Washington, DC: U.S. Government Printing Office.

Orent-Keiles, E. 1941. The role of boron in the diet of the rat. Proc. Soc. Exp. Biol. Med. 44:199-202.

Owen, E.C. 1944. The excretion of borate by the dairy cow. J. Dairy Res. 13:243-248.

Pfeiffer, C.C.; Hallman, L.F.; Gersh, I. 1945. Boric acid ointment. A study of possible intoxication in the treatment of burns. J. Am. Med. Assoc. 128:266-274.

Pierce, F.D.; Brown, H.R. 1976. Microgram determination of boron in surface waters by atomic emission spectrometry. Anal. Chem. 48:670-673.

Pinto, J.; Huang, Y.P.; McConnell, R.J.; Rivlin, R.S. 1978. Increased urinary riboflavin excretion resulting from boric acid ingestion. J. Lab. Clin. Med. 92:126-134.

Ridgway, L.P.; Karnofsky, D.A. 1952. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. Ann. N.Y. Acad. Sci. 55:203-215.

Roe, D.A.; McCormick, D.B.; Lin, R-T. 1972. Effects of riboflavin on boric acid toxicity. J. Pharm. Sci. 61:1081-1085.

Rosen, F.S.; Haggerty, R.J. 1956. Toxic hazards: fatal poisoning from topical use of boric acid powder. N. Engl. J. Med. 255:53.

Rosky, L.P.; Goldstein, A.G.; Sklaire, M.W.; Blumberg, M.L. 1957. The effect of boric acid upon hematocrit and hemoglobin values when injected into chicken embryos at ninety-six hours of incubation. Proc. Pa. Acad. Sci. 31:172-181.

Roush, A.; Norris, E.R. 1950. The inhibition of xanthine oxidase by borates. Arch. Biochem. 29:344-347.

Rubenstein, A.D.; Musher, D.M. 1970. Epidemic boric acid poisoning simulating staphylococcal toxic epidermal necrolysis of the newborn infant: Ritter's disease. J. Pediatr. 77:884-887.

Sanusi, I.D.; Tio, F.O.; Manno, J.E. 1975. Pancreatic inclusions and its relation to boric acid poisoning: review of the literature and report of a case. Forensic Sci. 6:165-174.

Sax, N.I. 1984. Dangerous properties of industrial materials. 6th Edition. New York: Van Nostrand Reinhold Company. p.513.

Schlettwein-Gsell, D.; Mommsen-Straub, S. 1973. Ubersicht Spurenelemente in Lebensmitteln. IX. Bor. Int. J. Vitam. Nutr. Res. 43:93-109.

Schroeder, H.A.; Mitchener, M. 1975. Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. J. Nutr. 105:452-458.

Seal, B.S.; Weeth, H.J. 1980. Effect of boron in drinking water on the male laboratory rat. Bull. Environ. Contam. Toxicol. 25:782-789.

Sherman, D.H.; Fox, F.J., Jr. 1955. A quantitative study of the cellular components in the peripheral circulation of chick embryos treated with boric acid at ninety-six hours of incubation. Proc. Pa. Acad. Sci. 29:94-105.

Select Committee on GRAS Substances. 1980. Evaluation of the health effects of borax and boric acid as food packaging ingredients. SCOGS-II-4. Report prepared for the Bureau of Foods, Food and Drug Administration, Washington, DC under Contract No. FDA 223-78-2100 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD. 30p. Available from: National Technical Information Service, Springfield, VA. PB81-121410.

Sittig, M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd Edition. Park Ridge, NJ: Noyes Publications. p.137-139.

Skipworth, G.B.; Goldstein, N.; McBride, W.P. 1967. Boric acid intoxication from "medicated talcum powder." Arch. Dermatol. 95:83-86.

Snyder, W.S.; Cook, M.J.; Nasset, E.S.; Karhausan, L.R.; Parry Howells, G.; Tipton, I.H. 1975. Report of the Task Group on Reference Man. International Commission on Radiological Protection. No. 23. New York: Pergamon Press.

Sprague, R.W. 1972. The ecological significance of boron. Los Angeles: The Ward Ritchie Press, United States Borax and Chemical Corp. 54pp.

Stein, K.M.; Odom, R.B.; Justice, G.R.; Martin, G.C. 1973. Toxic alopecia from ingestion of boric acid. Arch. Dermatol. 108:95-97.

Stokinger, H.E. 1981. The halogens and the nonmetals boron and silicon. In: Clayton, G.D.; Clayton, F.E., editors. Patty's industrial hygiene and toxicology. New York: Johns Wiley & Sons. p.2937-3043.

Tan, T.G. 1970. Occupational toxic alopecia due to borax. Acta Dermatovener (Stockholm) 50:55-58.

Tarasenko, N.I.; Kasparov, A.A.; Strongina, O.M. 1972. [The effect of boric acid on the male generative function.] Gig. Tr. Prof. Zabol. (11):13-16. (In Russian).

Teresi, J.D.; Hove, E.; Elvehjem, C.A.; Hart, E.B. 1944. Further study of boron in the nutrition of the rat. Am. J. Physiol. 140:513-518.

Tipton, I.H.; Stewart, P.L.; Martin, P.G. 1966. Trace elements in diets and excreta. Health Phys. 12:1683-1689.

Underwood, E.J. 1977. Trace elements in human and animal nutrition. 4th ed. New York: Academic Press. p.436-437.

U.S. Environmental Protection Agency. 1977. Multimedia environmental goals for environmental assessment. Vol. 1. EPA-600/7-77-136a.

Valdes-Dapena, M.A.; Arey, J.B. 1962. Boric acid poisoning. Three fatal cases with pancreatic inclusions and a review of the literature. J. Pediatr. 61:531-546.

Verbitskaya, G.V. 1975. [Experimental and field studies for the hygenic assessment of drinking water containing boron.] Gig. Sanit. (7):49-53. (In Russian).

Wang E.M. 1984. [Toxic effect of boron on laboratory rats]. Chung-Hau Yu Hang I Hsueh Tas Chih. 18:20-22. (In Chinese).

Watson, E.H. 1945. Boric acid: a dangerous drug of little value. J. Am. Med. Assoc. 129:332-333.

Weast, R.C., editor. 1983-1984. CRC handbook of chemistry and physics. 64th ed. Boca Raton, FL: CRC Press. p.B-7.

Weeth, H.J.; Speth, C.F.; Hanks, D.R. 1981. Boron content of plasma and urine as indicators of boron intake in cattle. Am. J. Vet. Res. 42:474-477.

Weir, R.J.; Fisher, R.S. 1972. Toxicolgic studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23:351-364.

Weser, U. 1966. Inhibition of adrenaline action on liver dephospho-phosphorylase by borate. Biochim. Biophys. Acta 12:413-416.

Weser, U. 1967. Stimulation of rat liver RNA synthesis by borate. Proc. Soc. Exp. Biol. Med. 126:669-671.

Windholz, M., editor. 1976. The Merck index, 9th ed. Rahway, NJ: Merck & Co., Inc. p.173, 1110.

Zittle, C.A. 1951. Reaction of borate with substances of biological interest. Adv. Enzymol. 12:493-527.

Zittle, C.A.; Della Monica, E.S. 1950. Effects of borate and other ions on the alkaline phosphatase of bovine milk and intestinal mucosa. Arch. Biochem. 26:112-122.

Zook, E.G.; Lehman, J. 1965. Total diet study: content of ten minerals: aluminum, calcium, phosphorus, sodium, potassium, boron, copper, iron, manganese, and magnesium. J. Assoc. Off. Anal. Chem. 48:850-855.

APPENDIX C

MOLYBDENUM

I. INTRODUCTION

Molybdenum has been identified as a potential substance-of-concern in agricultural drainage waters from the west side of the San Joaquin Valley and a moderate water quality concern in the San Joaquin River (Hansen and Morehardt, 1987). These determinations were based on standards for a continuous maximum of 0.044 ppm to protect aquatic life and a continuous agricultural maximum of 0.01 ppm to protect sensitive crops set by the state of California (State Water Resources Control Board, 1987). Estimates of the highest median concentrations of molybdenum in ground waters, surface runoff waters, and river water in different areas of the San Joaquin Valley (0.029, 0.08, and 0.005 ppm, respectively) do not all exceed the established limits, but the highest annual 95th percentile values do (0.48, 0.12, and 0.03 ppm, respectively) (Hansen and Morehardt, 1987).

II. OCCURRENCE

A. Natural

Molybdenum is a metal of the second transition series which is present in the earth's crust at levels of 1.0 to 1.5 ppm (Venugopal and Luckey, 1978; Windholz, 1976). Its abundance is equivalent to that of tungsten and is about ten times less than that of chromium (Parker, 1986) Molybdenum does not occur naturally in the metallic state, but is always found in association with other elements such as sulfur, oxygen, tungsten, lead, uranium, iron, magnesium, cobalt, vanadium, bismuth, and calcium (Jarrell et al., 1980). It is obtained from the ores molybdenite (MoS_2), wulfenite ($PbMoO_4.8H_2O$), powellite ($CaMoO_4$), ferrimolybdate ($Fe_2(MoO_4)_3$), and jordicite (amorphous molybdenum disulfide) (Friberg and Lener, 1986; Jarrell et al., 1980; Weast, 1983-1984). The majority occurs in the form of molybdenite, which is commonly associated with copper ores (Stokinger, 1981). Molybdenum is found in many parts of the world, but the richest deposits are in the Western Hemisphere. The United States contributes a major share (Stokinger, 1981). Geologically the highest concentrations of molybdenum have been found to be associated with sedimentary materials such as basaltic rocks, sandstones, calcareous clays and shales, and black shales (Jarrell et al., 1980). Generally, higher concentrations have been detected in sedimentary than in igneous rocks. Molybdenum is often found to be associated with the organic matter in sedimentary rock (Jarrell et al., 1980). The greatest geological enrichments occur in asphalts and crude oil.

Trace amounts of molybdenum are found in most of the natural waters of the world. The mean concentration in sea water is reported to be approximately 10 ug/L and similar amounts are assumed to occur in fresh waters, although local conditions and pollution can contribute to higher levels in water and sediments (Parker, 1986).

B. Anthropogenic

Molybdenum has a variety of industrial applications, with the primary use in steel alloys. It contributes to the hardening and toughness of quenched and tempered steels, as well as improving the strength of steel at high temperatures and reducing corrosion (Jarrell et al., 1980; Weast, 1983-1984). Molybdenum sulfide is used as a lubricant, especially in high temperature situations that would cause oils to decompose (Weast, 1983-1984). Other uses of various molybdenum compounds include catalysts, chemical reagents, and pigments. Molybdenum compounds are added to soil, plants, and water to achieve various enrichment or balance effects in plant and animal nutrition (Friberg and Lener, 1986). Molybdenum is added in trace amounts to fertilizers to stimulate plant growth (Goyer, 1986), most commonly in the forms of sodium and ammonium molybdate and molybdenum trioxide (Katyal and Randhawa, 1983).

Three major sources of molybdenum enrichment in the environment are release from industrial or mining operations, coal resource development, and municipal sewage sludge (Jarrell et al., 1980).

III. ENVIRONMENTAL FATE

A. Chemical Forms

More than 50 inorganic forms of molybdenum are known and organometallic forms also exist. Molybdenum is a typical transition element exhibiting a variety of valence forms. The most important oxidation states are +2, +3, +4, and +6, of which the last is the most stable (Stokinger, 1981). Some of the more common molybdenum compounds are ammonium molybdate, calcium molybdate, molybdic oxide, sodium molybdate, molybdenum disulfide, and molybdenum trioxide (Friberg and Lener, 1986). Ammonium and sodium molybdate are readily soluble in water; molybdic oxide is slightly soluble in water (Stokinger, 1981).

Molybdenum forms an extremely complicated series of compounds. With the exception of the oxides, sulfides, and halides, few simple salts of molybdenum are known. Molybdenum compounds readily disproportionate to yield mixtures containing various valence states with the strong tendency to form complex compounds. Shifts between different coordination numbers can result from relatively minor differences in conditions (Stokinger, 1981).

Above pH 6, the predominant form of molybdenum(VI) is the molybdate ion (MoO_4^{2-}), which can form stable salts with alkaline metal ions and insoluble salts with alkaline earth and transition metal ions (Parker, 1986). Hexavalent molybdenum complexes preferentially with oxygen and forms stable isopoly and heteropoly acids and salts:

$$(MoO_4)^{2-} \xrightleftharpoons{H+} Mo_2O_7 \xrightleftharpoons{2e} H_2(MoO_4)_6 \xrightleftharpoons{10e} H_2(Mo_2O_7)_6 \xrightleftharpoons{10e} (MoO_3)X$$

These polyacids can react with phosphates and tartrates in biological fluids and tissues. Molybdenum also binds to carboxyl groups, hydroxyl groups, and sulfhydryl groups in macromolecules (Venugopal and Luckey, 1978). This ability to form complexes with biologically active material in plants and animals is an important factor in molybdenum's role in living systems (Parker, 1986).

B. Availability to Plants

The molybdenum content of soils has been reported typically to range between 0.6-3.5 ppm, with a mean of approximately 2 ppm (Katyal and Randhawa, 1983). Lener and Bibr (1984) considered soil molybdenum concentrations between 0.2 and 0.7 ppm to be normal. Friberg and Lener (1986) reported the molybdenum content of normal soils to vary between 0.1 and 10 ppm. Kubota (1977) found that molybdenum concentrations in U.S. soils ranged from 0.08 to greater than 30 ppm, with a median value slightly more than 1 ppm. He also observed a striking pattern of increasing molybdenum concentrations from the eastern to the western United States.

The molybdenum content of soil varies with the molybdenum content of the parent material and is often higher in soils than in the parent material (Jarrell et al., 1980). High molybdenum contents in soils have been associated with sedimentary parent materials, especially shales (Jarrell et al., 1980). Shale and granite are rock sources of soil molybdenum in the western United States; the sandy materials of glacial and marine origin in the east contain much less of the element (Kubota, 1977).

Most plants grow poorly in molybdenum-deficient soils and will usually respond to supplementation. Legumes and crucifers have especially high molybdenum requirements, and are affected by molybdenum deficiencies in soils in which cereals and grasses can grow easily (Katyal and Randhawa, 1983). Citrus has a higher requirement for molybdenum than other orchard plants (Jarrell et al., 1980). Crop plants can tolerate very high concentrations of molybdenum in the soil without growth depression or other symptoms of toxicity, but high contents in forages can cause disorders in animals (Katyal and Randhawa, 1983).

Katyal and Randhawa (1983) have summarized the conditions leading to molybdenum deficiency or excess in plants as follows: Molybdenum deficiency occurs in

- acid soils
- leached, sandy soils
- soils with high free-iron oxide
- soils low in phosphorus and copper and high in sulfate.

Plants build up toxic levels of molybdenum in

- alkaline soils
- poorly drained soils
- soils with low levels of sulfate and copper and high availability of phosphorus
- soils treated indiscriminantly with molybdenum fertilizers.

The total molybdenum content of soil bears little relation to its availability to plants. The form in which molybdenum occurs in soils is one important determinant of availability. As noted by Katyal and Randhawa (1983) molybdenum can occur in minerals and in the silicate structures of mineral feldspars and micas, and in these forms is highly insoluble. Molybdenum in acid soils exists in close association with sesquioxides and is unavailable to plants. Molybdenum also is present as an anion (MoO_4^{2-}) on the surface of soil particles and in organic compounds, which are both available to plants. The content of dissolved molybdenum in the soil is low and is dependent on pH, increasing in alkaline conditions (Katyal and Randhawa, 1983).

The availability of molybdenum in the soil to plants has been found to be dependent on several factors including soil pH, organic content, texture, moisture, temperature, and nutrient interactions (Katyal and Randhawa, 1983). Molybdenum is highly available in alkaline soils (in contrast to most essential micronutrients) but is retained very strongly in soils in the pH range 3 to 5 (Barrow, 1977; Misra et al., 1977). Maximum release of retained molybdenum occurred at pH 5 to 8.5 (Misra et al., 1977). Liming has been shown to increase molybdenum availability and to alleviate deficiency in acid soils. Molybdenum availability to plants has been observed to vary positively with the organic content of soils (Misra et al., 1977). Sandy soils retain molybdenum less well than soils with heavy textures and are therefore more likely to exhibit molybdenum deficiency (Katyal and Randhawa, 1983). Molybdenum availability increases with soil moisture content; with few exceptions, molybdenum accumulation in plants to levels toxic to animals occurs only on poorly drained soils (Allaway, 1977). High temperatures accelerate the conversion of adsorbed molybdate to more firmly bound forms and thus may decrease molybdenum availability (Barrow, 1977). A high content of phosphorus favors the uptake of molybdenum, but high sulfate, copper, aluminum, and iron are antagonistic to molybdenum uptake from soils (Jarrell et al., 1980; Katyal and Randhawa, 1983).

C. Mobility

Parker (1986) has summarized in general terms the mobility of molybdenum in the environment (see Table C.1).

Industrial activities have also been responsible for enriching urban atmospheres with molybdenum, but concentrations are lower than those of many other trace elements (Jarrell et al., 1980; Schroeder, 1971). Atmospheric molybdenum appears to be available to biological systems (Jarrell et al., 1980).

The concentration of molybdenum in plants varies greatly and is influenced by the molybdenum availability in soils. Typical concentrations of molybdenum in plants range from 0.1 to 2.0 ppm according to Katyal and Randhawa (1983), but levels up to 300 ppm have been detected. Kubota (1977) found a pattern of increasing molybdenum concentrations in legumes from the eastern United States (median about 0.5 ppm) to the western United States (median of 6 ppm). This pattern roughly followed the distribution of acid soils in the east to neutral or alkaline soils in the west.

The molybdenum content of various plant parts varies, with higher concentrations in the interveinal areas than in the mid rib, stems, or margins of the leaves (Allaway, 1977; Katyal and Randhawa, 1983). Different plant

Table C.1. Transfer of molybdenum in the environnment (adapted from Parker, 1986)

Loss from soils	from →	Weathering Plant uptake Mining	to →	Plants Natural waters Manufacturing
Loss from plants	from →	Animals Decay Harvesting	to →	Animals Soil Natural Waters Humans
Loss from natural waters	from →	Animals Plants Sedimentation	to →	Animals Plants Soils
Loss from animals	from →	Animals Decay Sewage	to →	Humans Soil Natural waters
Gain for soils	from →	Weathering Plants Animals Manufacturing discharge		
Gain for plants	from →	Soil Natural waters		
Gain for natural waters	from →	Weathering Plants Animals Manufacturing discharge		
Gain for animals	from →	Plants Natural waters Manufacturing discharge		

species accumulate differential amounts of molybdenum under the same conditions: legumes normally contain more molybdenum than do grasses grown on the same soil, and crucifers such as broccoli and cauliflower normally contain higher levels than other plants in the same area (Allaway, 1977).

Molybdenum is present in plant tissues at concentrations one order of magnitude less than concentrations of other elements required for plant growth (Allaway, 1977). Plants are generally considered to be deficient in molybdenum when they contain less than 0.1 ppm (on a dry matter basis) (Jarrell et al., 1980). Although high levels of molybdenum are not toxic to plants (Hornick et al., 1977), levels in forages in excess of 15 ppm can produce toxicity in ruminant animals (Katyal and Randhawa, 1983).

Molybdenum concentrations in animal tissues are generally lower than in plant tissues and vary with the intake of molybdenum as well as copper and sulfate. Molybdenum occurs in concentrations similar to manganese in all tissues and fluids of the animal body (Underwood, 1977).

The molybdenum content of cow's milk is highly dependent on the dietary intake of the animals with "normal" levels reported to range from 18-120 ug/L (Underwood, 1977). Reported intakes by humans are diet-dependent. Foods vary in their molybdenum content; legumes, whole cereal grains, leafy vegetables, liver, and kidney are good sources while fruits, root and stem vegetables, refined grain products, sugars, oils and fats, muscle meats, and dairy products are poor sources (Berman, 1980; Hazell, 1985; Schroeder et al., 1970; Westerfeld and Richert, 1953).

IV. ESSENTIALITY/BIOLOGICAL FUNCTION

Molybdenum is an essential element for microorganisms, plants, and animals including man. Species of every living system have been found to contain molybdenum-dependent enzymes. The functions of a wide variety of molybdoenzymes have been reviewed by Rajagopalan (1984).

Molybdenum is necessary for the fixation of nitrogen in the soil by bacteria and by nitrogen-fixing plants because of its function in two major enzymes, nitrogenase and nitrate reductase. Nitrogenase, found in plants such as beans, clover, alfalfa, and other legumes, catalyzes the conversion within the plant of nitrogen to ammonia (Schrauzer, 1976). Nitrate reductase, found in nonleguminous plants, bacteria, and fungi, catalyzes the conversion of nitrate ion to nitrite ion, a first step in the assimilation of nitrogen.

Xanthine oxidase/dehydrogenase catalyzes the conversion of xanthine to uric acid, an important step in the metabolism of purine-based compounds (Mahler and Green, 1954). It is a complex enzyme containing a molybdenum subunit, a flavin adeninedinucleotide portion, and two iron-sulfur centers. The importance of molybdenum to the function of xanthine oxidase in animals was first recognized by De Renzo et al. (1953) and Richert and Westerfeld (1953). Another important molybdenum-containing enzyme in animals is sulfite oxidase, which catalyzes the conversion of sulfite ion to sulfate ion, a final step in the degradation of sulfur-containing amino acids and a protective reaction against sulfur dioxide toxicity (Cohen et al., 1973; Gunnison et al., 1987; Johnson et al., 1974). The molybdenum cofactor is apparently the same in these two, and other, molybdoenzymes.

Lener and Bibr (1984) have summarized the limited number of reports of molybdenum deficiency in the field in lambs and chicks. Molybdenum deficiency is difficult to induce experimentally; feeding large amounts of the antagonist tungsten is usually required to produce molybdenum deficiency symptoms in rats (Higgins et al., 1956; Johnson and Rajagopalan, 1976). [Simultaneous feeding of small amounts of molybdenum counteracts the effects of tungsten suggesting that molybdenum deficiency rather than tungsten toxicity is responsible for the observed effects (Rajagopalan, 1987).] Such studies indicate that the production of molybdenum deficiency in adult rats does not cause any detectable physical ill effects despite marked decreases in tissue molybdoenzyme activities, but that the absence of molybdenum may result in abnormalities during the early developmental stages (Rajagopalan, 1987).

Molybdenum deficiency has not been detected in any normal human population. The only natural occurrence of molybdenum deficiency in humans has resulted from the genetic deficiency of the molybdenum cofactor in several severely ill children (Chan and Rennert, 1985). All of these children exhibited combined deficiencies of aldehyde dehydrogenase, sulfite oxidase, and xanthine dehydrogenase (with increased excretion of sulfite, thiosulfate, S-sulfocysteine, hypoxanthine, and xanthine), and displayed marked neurological abnormalities, dislocation of the lens, and mental retardation (Chan and Rennert, 1985; Rajagopalan, 1984). Supplementation of the diet with molybdenum did not reverse the abnormalities. Isolated xanthine oxidase and sulfite oxidase deficiencies on a genetic basis have also been reported (Anonymous, 1987); the former is a relatively benign disorder, while the latter is a crippling neurological disease with the same symptoms as the combined genetic deficiency.

The first demonstration of a diet-induced deficiency of molybdenum in humans occurred as a result of prolonged total parenteral nutrition (TPN) with a solution low in molybdenum (Abumrad et al., 1981; Anonymous, 1987; Rudman and Williams, 1985). The affected patient was a young man with Crohn disease and a short gut of 12 years' duration who had been receiving TPN for 18 months. The patient experienced episodes of tachycardia, tachypnea, central scotomas, night blindness, lethargy, and coma while on TPN; these symptoms resolved when TPN was discontinued. Biochemical abnormalities during symptomatic periods included high plasma methionine; low serum uric acid levels; increased urinary excretion of sulfite, thiosulfate, hypoxanthine and xanthine; and decreased urinary excretion of uric acid and inorganic sulfate. Treatment with ammonium molybdate (300 ug/day) improved the patient's clinical condition and reversed the biochemical abnormalities.

Based on a number of epidemiological studies [summarized by Friberg and Lener (1986)], molybdenum has also been proposed to exert a cariostatic effect. However, an inverse correlation between molybdenum exposure and the incidence of caries was not demonstrated in a population in the United States (Curzon et al., 1971). Results of animal experiments were also contradictory (Hadjimarkos, 1973). Despite studies that suggested a feasible mechanism to explain an effect of molybdenum on caries resistance (Solomons et al., 1973), this hypothesis seems to have been discounted.

V. TOXICOKINETICS

A. Absorption from Gastrointestinal Tract, Lung, Skin

Gastrointestinal absorption of molybdenum compounds (from most diets and with most inorganic forms) is high in animals and humans (Underwood, 1976). Hexavalent and water-soluble forms of molybdenum are well absorbed by cattle (Underwood, 1976). Hexavalent molybdenum absorption from the gastrointestinal tract in a variety of experimental animals ranges between 40 and 85% (Friberg and Lener, 1986). Fairhall et al. (1945) confirmed the rapid absorption of molybdenum trioxide administered orally to guinea pigs and rabbits. Radiolabelled molybdic oxide was used by Neilands et al. (1948) to demonstrate that approximately 84% of an oral dose was absorbed in the gastrointestinal tract of rats, and that simultaneous oral administration of copper reduced molybdenum absoprtion to 75%. Kosarek and Winston (1977) gave oral doses of molybdenum in the form of molybdate to rats starved for 24 hours and found the net absorption to be very efficient with 2.73, 1.86, and 1.26% remaining unabsorbed from doses of 38, 100, and 380 g. Absorption was completed within 6 hours, with a half-life of 0.86 hours. Van Campen and Mitchell (1965) gave rats oral doses of 2.7 umoles molybdenum as sodium molybdate and found that the metal was absorbed from both the stomach and intestine. The various ligated intestinal segments (duodenum, mid-section, or ileum) were sites of greater absorption than the stomach, with relatively little difference between the segments. Winston et al. (1985) found that in rats molybdenum (as sodium molybdate) was absorbed more rapidly when dissolved in water than when mixed in food, and that organically bound molybdenum was absorbed more slowly than either added form.

In a balance study based on analyses of food, feces, and urine of two men consuming an average of 210 and 460 ug Mo/day over a 50-week period, Tipton et al. (1969) found that gastrointestinal absorption of molybdenum was greater than 50%. From the balance data obtained from four young women in a metabolic study of 27 days by Robinson et al. (1973) absorptions of 30-60% may be estimated (subjects consumed an average of 48, 46, 91, and 96 ug Mo/day). Apparent absorptions of 63-78% were observed in a number of metabolic balance studies of preadolescent girls by Engel et al. (1967). In a 3-day balance study with healthy children, Alexander et al. (1974) found that 77% of the molybdenum in a diet supplying 3.02 ug/kg body weight/day was absorbed and 42% retained per day.

Exposure via inhalation resulted in appreciable absorption of hexavalent forms of molybdenum, but not molybdenum disulfide, in guinea pigs (Fairhall et al., 1945). Friberg and Lener (1986) report that data are not available on absorption of molybdenum after inhalation in humans. Walravens et al. (1979) concluded that molybdenum was assimilated by workers exposed to molybdenum-containing dust, but could not determine whether molybdenum was absorbed through the lung or by the gastrointestinal tract upon swallowing of secretions.

No data on absorption via skin were found.

B. Distribution

Determination of molybdenum in lungs, liver, kidney, spleen, and bone of guinea pigs following 25 days of inhalation of sub-LD_{50} doses of molybdenum sulfide, the dust and fume of molybdenum trioxide, and calcium molybdate showed rather uniform distribution in all tissues (Fairhall et al., 1945). Values from 1 to 6 ug/g fresh tissue were common for all compounds except molybdic oxide and calcium molybdate dusts, which were two- to four-fold higher in the kidney, lung, spleen, and bone. Higher retentions in lung than in other tissues (40 and 18 times, respectively) were observed for the sulfide and the molybdate.

After a single oral administration of molybdenum trioxide to guinea pigs, rapid accumulation of molybdenum was detected in the kidneys, liver, and bone (Fairhall et al., 1945). In mice, 1 to 24 hours after a single intravenous injection the highest concentrations of molybdenum were found in the kidneys, liver, and pancreas (Rosoff and Spencer, 1973). The level remained constant in the liver during the observation period, but levels in the kidney and pancreas declined.

The concentration of molybdenum in kidney, liver, intestine, spleen, testis, muscle, skin, blood, bone, and teeth of rats reached a maximum within 1-2 hours after the subcutaneous administration of graded doses of ammonium molybdate labeled with ^{99}Mo (Bibr and Lener, 1974). Fourteen days later, most of the administered molybdenum was present in the kidneys, liver, hard tissues, and skin, with the greatest retention in skin and teeth; concentrations in tissue were dose-dependent. Pentavalent molybdenum disappeared more slowly than hexavalent molybdenum from the blood, liver, and jejunoileocecum of rats given a single intravenous injection (Lener and Bibr, 1979).

Molybdenum has been shown to react with connective tissue and to alter the metabolism and mechanical properties of collagen (Lener et al., 1976). Molybdenum also has been reported to accumulate in long bone in growth cartilage and in diaphysis spongiosis (Friberg and Lener, 1986). The maximum concentration in teeth has been detected in dentin, cement, and to a lesser extent in enamel (Friberg and Lener, 1986). Molybdenum has also been found in the hair and hooves of cattle and the wool of sheep (Cunningham and Hogan, 1958).

In the blood, molybdenum is bound in the form of molybdate to alpha-2-macroglobulin and to the proteins of the erythrocyte membrane (Kselikova et al., 1974, 1977; Lener et al., 1979).

After administration of molybdenum to rats in drinking water for four generations, the concentration was found to be higher in the tissues of males than females (Kosarek and Winston, 1975).

Normal values for the molybdenum contents of various tissues in animals and humans [based on studies by Higgins et al. (1956) and Tipton and Cook (1963)] are given in Table C.2 below:

Table C.2. Normal molybdenum concentrations in animal tissues in ppm on a dry-weight basis (adapted from Underwood, 1977)

Species	Liver	Kidney	Spleen	Lung	Brain	Muscle
Adult human	3.2	1.6	0.20	0.15	0.14	0.14
Adult rat	1.8	1.0	0.52	0.37	0.24	0.06
Chicken	3.6	4.4	-	-	-	0.14

C. Excretion

Animal data have indicated that little molybdenum is retained and most is excreted, primarily via urine, during the first two weeks after single exposures by various routes in guinea pigs, rats, and swine (Bell et al., 1964; Bibr and Lener, 1973; Fairhall et al., 1945; Kselikova et al., 1974; Neilands et al., 1948). In rats, the extent and rapidity of urinary excretion increased with increasing dose of ammonium molybdate administered via intragastric or subcutaneous routes (Bibr and Lener, 1973). The main route of excretion in cows was reported to be feces (Bell et al., 1964). Biliary excretion was also demonstrated in rats after intravenous injection of both hexavalent and pentavalent forms of molybdenum (Lener and Bibr, 1979). Small amounts are excreted via milk and hair, and negligible amounts via saliva (Friberg and Lener, 1986).

Molybdenum excretion has been shown to be influenced by copper and sulfate (Dale et al., 1973; Dick, 1953). Huisingh and Matrone (1976) have indicated that sulfate can compete with molybdenum for protein carriers and can enhance molybdenum excretion by inhibiting tubular reabsorption.

Rosoff and Spencer (1964) studied excretion of molybdenum in human subjects after a single intravenous injection of radiolabeled molybdenum. The excretory patterns varied in different subjects. The 5-day cumulative urinary excretion of ^{99}Mo ranged from 16.6 to 27.2% in four patients. The 10-day cumulative excretions in two subjects were 24 and 29% in urine and 6.8% and less than 1% in feces.

The total excretion of molybdenum under steady-state conditions in humans has not been determined, but data from Tipton et al. (1969) suggest that 25-50% of the ingested amount is excreted in urine.

The biological half-time of most of absorbed molybdenum was reported by Friberg (1979) to be on the order of hours to a maximum of about one day in laboratory animals, based on the studies of Fairhall et al. (1945) and Neilands et al. (1948), and up to two weeks in humans, based on the data of Rosoff and Spencer (1964).

VI. TOXICITY

A. Animals

The effects on animals of excess molybdenum depend on the species and age of the animal; the amount and chemical form of the molybdenum; the copper intake and status of the animal; the dietary intake of inorganic sulfate and total sulfur, as well as substances such as protein, cystine, and methionine which may be oxidized to sulfate in vivo; and the level of intake of other metals. Relatively little information on the toxicity of molybdenum in common laboratory animals has been published in the literature; most attention has been devoted to molybdenum toxicity in ruminant livestock. The first recognition of the toxicity of molybdenum was in cattle grazing on "teart" pastures (where the forage contained very high levels of molybdenum) in England (Fergusen et al., 1938, 1943). These animals rapidly developed a disorder, characterized by severe diarrhea and loss of condition, which could be reversed by copper supplementation (Underwood, 1977). Sheep were found to be less sensitive than cattle but also adversely affected by high-molybdenum forage (Underwood, 1976). The complex interactions of molybdenum, copper, and sulfate in producing toxicity symptoms and biochemical changes in ruminants were recognized early (Cunningham et al., 1959; Dick, 1953, 1954). Molybdenum toxicity and interactions in ruminants have been reviewed (Buck and Ewan, 1973; Huisingh and Matrone, 1976; Pitt, 1976; Ward, 1978) and will be discussed further in Sections VI-F and VI-G. In the following sections, attention will be given to the toxic consequences of excess molybdenum in monogastric animals.

1.Acute/short-term exposures

By inhalation or oral routes, molybdenite was found by Fairhall et al. (1945) to produce essentially no toxicity. Guinea pigs exposed 1 hr daily for 25 days at 490 mg/m^3 of molybdenite ore (230 mg Mo/m^3) showed only increased respiration. Rats ingesting as much as 500 mg daily for 44 days showed no toxic effects and all gained weight. Guinea pigs given intraperitoneal injections with 800 mg/kg showed 17% mortality in 4 days and 25% mortality in 4 months; survivors remained apparently healthy and gained weight, possibly indicating a physical effect from the mass injection rather than toxicity of the metal.

By contrast, all hexavalent compounds tested (molybdic oxide, ammonium molybdate, and sodium molybdate) were increasingly fatal over the same dose range (Fairhall et al., 1945). All oral daily doses in excess of 100 mg/day were uniformly fatal. The approximate LD$_{50}$s of daily repeated doses were 100, 125, and 330 mg Mo/kg body weight for calcium molybdate, molybdic oxide, and sodium molybdate, respectively.

Molybdic oxide dust was extremely irritating to guinea pigs on daily, repeated, 1-hour exposures at 250 mg/m^3 (164 mg Mo/m3) (Fairhall et al., 1945). Signs of toxicity included loss of appetite, weight loss, diarrhea, muscular incoordination, and alopecia. Of 51 animals exposed, 26 died after the tenth exposure. Exposure to MoO$_2$ fume under the same conditions was substantially less toxic, with only 8.3% mortality compared to 51% mortality with the dust. Inhalation of calcium molybdate dust under the same conditions proved fatal to 20.8% of 24 guinea pigs, without showing any signs of toxicity.

Unpublished results of acute toxicity tests with various molybdates in laboratory animals performed for Climax Molybdenum between 1957 and 1963 [summarized by Stokinger (1981)] showed that calcium and zinc molybdates were "practically nontoxic" orally, percutaneously, and by inhalation, based on single or brief exposures. These two molybdates caused no irritation to intact or abraded skin and no significant eye irritation in the standard rabbit test. Sodium molybdate did cause primary irritation at 24 hr which cleared by 72 hr.

The acute toxicity of various molybdenum compounds is summarized in Table C.3 below.

Neilands et al. (1948) found that feeding molybdenum (as sodium molybdate) in a purified diet at a level of 5000 ppm resulted in the deaths of weanling rats after one week. Levels of 1000 and 500 ppm fed for four weeks permitted a greatly reduced rate of growth, without apparent gross pathological or hematological changes. The toxicity of a diet containing 400 ppm molybdenum and 77 ppm copper could be prevented by supplementation with an additional 20 ppm copper. Gray and Ellis (1950) found similar results feeding rats molybdenum added to a purified diet or to a commercial ration at levels ranging from 40 to 4000 ppm. They also observed that supplemental zinc exacerbated the growth depression caused by molybdenum toxicity. The addition of supplemental copper or methionine to a purified diet containing 800 ppm molybdenum alleviated much of the toxicity observed with molybdenum alone (Gray and Daniel, 1954). In addition to growth depression, other symptoms of molybdenosis seen in rats included achromotrichia and alopecia, male sterility, reduced lactation (Jeter and Davis, 1954), and mandibular and maxillary exostoses (Ostrom et al., 1961; Van Reen, 1959). In molybdenotic rats, alkaline phosphatase activity was decreased in the liver and increased in the kidney and intestine (Williams and Van Reen, 1956); liver sulfide oxidase activity was markedly depressed, but the activities of liver cysteine desulfhydrase and kidney aryl sulfatase were not affected (Mills et al., 1958).

When rabbits were fed a commercial diet supplemented with molybdenum (as sodium molybdate) at levels of 1000 ppm or more a severe toxicity syndrome characterized by anorexia, weight loss, alopecia, dermatosis, anemia, and death occurred (Arrington and Davis, 1953). Some animals also developed a deformity of the front legs. Toxicity symptoms could be prevented or reversed by addition of copper to the ration. Other findings in molydenotic rabbits include epiphyseal line fractures (McCarter et al., 1962), decreased erythrocyte survival time (Robinson et al., 1969), and thyroid hypofunction (Widjajakuma et al., 1973).

The growth of chicks and poults was reduced approximately 25% by the addition of 300 ppm molybdenum (as sodium molybdate) to practical starter rations (Kratzer, 1952). There was no evidence of anemia, diarrhea, or changes in feathers in the birds. Addition of copper to the molybdenum-containing rations produced only slightly improved growth. Similar findings were reported by Arthur et al. (1958) when chicks were fed molybdenum at levels of 200, 350, and 500 ppm. At higher levels (4000 ppm or more of molybdenum) sodium molybdate did cause anemia in chicks (Davies et al., 1960). Ammonium molybdate was more toxic to chicks than the sodium salt; sulfate added to the diets of chicks at two times the level of molybdenum alleviated the symptoms of molybdenosis.

Table C.3. Acute molybdenum toxicity (adapted from Venugopal and Luckey, 1978)

				mg/kg body weight	
Compound	Animal	Route	Toxicity	Compound	Metal
Molybdenum trioxide	Rat	inhal	LD_{75}		287*
	Rat	oral	LD_{50}	188	125
	Guinea pig	ip	LD_{75}	400	267
Ammonium molybdate	Rat	oral	LD_{50}	680	370
	Rat	ip	MLD	203	110
	Guinea pig	oral	LD_{100}	2200	1200
	Guinea pig	sc	LD_{100}	1380	750
	Guinea pig	ip	LD_{100}	800	435
	Rabbit	oral	LD_{100}	1870	1020
	Rabbit	sc	LD_{100}	1600	870
	Cat	oral	LD_{100}	2400	1310
Disodium molybdate	Mouse	ip	LD_{50}	303	120
	Rat	ip	MLD	290	115
	Rat	ip	LD_{100}	385	153
	Rat	ip	LD_{50}	576	228
Calcium molybdate	Rat	ip	LD_{50}	208	99.8

* Exposure for 1 hour daily for 30 days (dose given in mg/m^3).

3. Chronic exposure

The symptoms of chronic molybdenum toxicity in animals include loss of weight, anorexia, anemia, impaired lactation, male sterility and testicular degeneration, osteoporosis, and bone-joint abnormalities (Venugopal and Luckey, 1978). These symptoms develop after fairly brief exposures (several weeks to several months); few toxicity studies in laboratory animals have been conducted for extended periods.

Winston et al. (1973) fed rats a commercial ration with 1-3 ppm molybdenum and provided deionized water with and without 10 ppm molybdenum (as sodium molybdate) as the sole source of drinking water. Five- to twelve-month-old rats so treated were subjected to cold stress by being placed at 2-3°C for four days; controls remained at room temperature. All of the cold-stressed animals lost weight, but the weight loss was twice as great in the molybdenum-treated rats. This study was the first to demonstrate a deleterious effect of molybdenum at such a low level and with adequate amounts of other nutrients in the diet.

In a similar experiment, male rats given 0, 5, or 10 ppm molybdenum (as sodium molybdate) in drinking water were subjected to heat stress (exposure to 37° for 16 hours) at 14-16 weeks of age (Winston and Trainor, 1978). All rats lost weight during the test period, but heat stress caused significantly greater losses. Groups treated with molybdenum lost significantly more weight, in a dose-related fashion, than those without added molybdenum. Serum glucose levels were increased by heat stress, but the greatest response was observed in the rats that received no supplemental molybdenum.

Winston et al. (1976) also studied adaptation to high levels of consumption of molybdenum in four generations of rats given 0, 10, 100, or 1000 ppm molybdenum in drinking water. In the first generation, reduced stress responses in a variety of tests were observed in all the molybdenum-treated groups; in the second and third generations, the differences became insignificant or disappeared. Molybdenum levels in the tissues of rats given the two highest levels of molybdenum declined in succeeding generations.

B. Human

1. Acute/short-term exposures

Molybdenum intoxication in humans has rarely been observed; acute poisoning appears to be quite uncommon. A short-term balance study with diets containing very high levels of molybdenum was conducted in India by Deosthale and Gopalan (1974). Men were fed diets containing two sorghums with different concentrations of molybdenum for periods of 10 days. The low-molybdenum sorghum diet supplied 166 ug/day; the high-molybdenum sorghum diet supplied 540 ug/day; and the high-molybdenum sorghum diet supplemented with ammonium molybdate supplied 1540 ug/day. Mean uric acid excretion in the urine was not increased by increasing the amount of molybdenum ingested; the excretions of calcium, phosphorus, and sulfate were also unchanged. In contrast, the excretion of copper in the urine was markedly increased with increasing molybdenum in the diet (the copper contents of the diets were similar). Serum concentrations of copper were also elevated when subjects consumed the sorghum diet with a higher content of molybdenum, suggesting mobilization of tissue copper or the inhibition of copper uptake by the tissues.

2. Chronic exposure

The earliest report of human toxicity resulting from chronic ingestion of high levels of molybdenum was that of Kovalsky et al. (1961) who studied a region in the Soviet Union (Armenia) with levels of 77 ppm molybdenum and 39 ppm copper in the soil. High molybdenum and low copper contents were observed in the agricultural products and drinking water of the region. Over 50% of the diet in the area was composed of locally produced products. The total daily intakes of molybdenum and copper by adults were estimated to be 10-15 mg and 5-10 mg, respectively, in the affected area, compared to 1-2 mg and 10-15 mg, respectively, in a control area. A medical survey of 400 residents in two villages in the affected region revealed incidences of a gout-like disorder of 31 and 18%, in contrast to a stated incidence of 1-4% in the general population. Symptoms of the disorder included arthralgia in the peripheral joints (knees, hands, and feet), joint deformities, and increased levels of uric acid in the blood and urine. Friberg and Lener (1986) have noted the difficulties in interpreting the results of this study, particularly with regard to possible bias introduced by the selection of groups to be compared. However, the results are consistent with the theoretical outcome of excess molybdenum consumption: high levels of molybdenum could give rise to increased activity of xanthine oxidase which in turn could cause increased formation of uric acid.

Walravens et al. (1979) studied workers chronically exposed to molybdenum-containing dust in a molybdenite roasting plant. Twenty-five male workers with an average age of 30.8 years (range, 19-59 years) and durations of employment ranging from 0.5-18 years were compared to a control group of 24 students and researchers with a mean age of 28.3 years (range, 19-44 years). The daily body burden of soluble molybdenum for the workers was estimated to be 10.2 mg based on the concentration in respirable dust. Assimilation of the molybdenum by the exposed workers was demonstrated by higher levels of molybdenum in the plasma (9-365 vs. 0-34 ng/ml) and urine (120-11,000 vs. 20-230 ug/L) than in the controls. The exposed workers also had marked elevations in serum ceruloplasmin and smaller increases in serum uric acid concentrations. No evidence of molybdenum-induced gout was detected in the responses to a medical questionnaire; only non-specific medical complaints were reported.

Industrial exposure of miners and metallurgy workers in the Soviet Union to air-borne concentrations of molybdenum between 60 and 600 mg/m^3 was reported by Eolian (1965) to result in an increased incidence of such non-specific signs of toxicity as weakness, fatigue, anorexia, headaches, joint and muscular pain, and tremor of the hands [summarized by Lener and Bibr (1984)].

A high incidence of bone deformities in the lower extremities was reported in a population in India whose diet consisted of large amounts of sorghum, which contained unusually large amounts of both molybdenum and fluorine (Anonymous, 1975). The osteoporosis produced by excess fluorine in this population has been assumed to be enhanced by the molybdenum.

C. Mutagenicity

Venitt and Levy (1974) found no evidence for the mutagenicity of soluble molybdenum salts in a bacteriological spot-test assay with several tryptophan-requiring strains of *Escherichia coli*.

Rossman et al. (1984), however, found that molybdate could elicit DNA damage in bacteria provided the exposures were carried out under conditions of long-term growth in subtoxic concentrations. Rossman and Molina (1986) assayed various metal salts for their ability to modulate ultraviolet-induced mutagenesis in *Escherichia coli* WP2. Sodium molybdate was found to be comutagenic (at concentrations higher than 100 M) in *E. coli* WP2 with normal DNA repair capabilities, but not in a repair-deficient strain of the bacteria.

D. Carcinogenicity

Maltoni (1974) reported the induction of subcutaneous sarcomas at the site of injection of the pigment molybdenum orange (lead chromate and molybdenum chromate); the number of tumors so produced was greater than the number caused by lead chromate alone, but chromium was considered to be the carcinogenic agent. Injection-site tumors are poor indicators of carcinogenic potential, however.

Shimkin et al. (1977) assayed various metal compounds for carcinogenic activity by the pulmonary tumor response in a susceptible, inbred strain of mice. The mice were injected intraperitoneally three times weekly for 6-24 injections at the maximum tolerated dose and were killed 30 weeks after the first injection. Molybdenum trioxide was judged to have a weakly carcinogenic effect based on a small but statistically significant increase in the number of tumors per mouse after its injection.

Orally ingested molybdenum has been found to offer some protection against chemical carcinogenesis. Male weanling Sprague-Dawley rats were fed ad libitum a semipurified diet and demineralized drinking water with and without the addition of molybdenum (a sodium molybdate) or tungsten (as sodium tungstate) (Luo et al., 1983; Yang et al., 1985). At levels of 2 or 20 ppm, molybdenum in the drinking water significantly inhibited the induction of esophageal and forestomach carcinogenesis in animals given doses of N-nitrosarcosine ethyl ester by gastric intubation. Tungsten at 200 ppm in water overcame the inhibitory effect of the low level of molybdenum (0.026 ppm) in the diet. In another experiment (Wei et al., 1985; Yang et al., 1985), virgin female Sprague-Dawley rats were fed the same diet and demineralized drinking water with 10 ppm molybdenum (as sodium molybdate) or 150 ppm tungsten (as sodium tungstate) and were given a single intravenous injection of 5 mg of N-nitroso-Nmethylurea. Molybdenum did not affect the incidence of mammary carcinoma at 125 days after injection, but after 198 days carcinoma incidence in the molybdenum-treated animals was significantly less (approximately half) than that in the control rats or the rats treated with tungsten. Animals treated with tungsten had an greater incidence of mammary carcinoma 125 days after injection than did untreated controls.

In a correlational epidemiologic study, Briese (1976) detected no association between the geographic variations in cancer mortality and incidence in Colorado and the molybdenum levels in surface waters.

E. Reproductive Toxicity

Very little data have been generated to assess the teratogenic potential or reproductive toxicity of molybdenum. Colmano (1973) showed that molybdenum added to the media of Euglena gracilis produced abnormal cell divisions and clustering with a teratogenic appearance. Reproductive function was found to be disrupted in rats fed very high levels of molybdenum (Jeter and Davis, 1954), but this impairment was due to male sterility rather than an effect on the embryos. Smaller litters were observed in female rats given drinking water containing 100 ppm molybdenum throughout their lifetimes than in rats given 10 ppm molybdenum in water.

F. Mechanism of Toxicity

In ruminants molybdenum toxicity is clearly related to copper depletion, but findings are not as straightforward in nonruminants. A single hypothesis has been advanced to rationalize the seemingly irreconcilable differences between species; it suggests that the copper antagonism of molybdenum may be effected through thiomolybdates (formed by the interaction of sulfur and molybdate) and that the major sites of thiomolybdate formation may differ in ruminants and nonruminants. Suttle (1980) has reviewed the (mainly indirect) evidence for this hypothesis and concluded the following:

- Similarities in the physiological effects of thiomolybdate and molybdate plus sulfate in ruminants suggest that thiomolybdate is formed in the sulfide-rich environment of the rumen.

- Ingestion of thiomolybdates by rats results in symptoms similar to molybdenum toxicity in ruminants (Spence et al., 1980).

- Qualitative similarities in the plasma copper distribution produced by high levels of molybdate in the rat and thiomolybdate in the ruminant suggest that a thiomolybdate-like species may also be formed at systemic sites in nonruminants.

- The contrasting effects of sulfur and the changes in tissue copper status in ruminants and rats may be explained in terms of the relative importance of gut and systemic sites of thiomolybdate formation. When the gut site predominates (ruminants), the absorption of both copper and molybdenum is impaired, causing tissue depletion that dietary sulfur can exacerbate by promoting thiomolybdate formation. When systemic sites predominate (rats), copper and molybdenum excretion is impaired, leading to tissue accretion that dietary sulfur can alleviate by depressing the absorption of molybdenum.

In a more recent review, Mason (1986) also concluded that the accumulating evidence supports the role of thiomolybdates in mediating molybdenum toxicity.

G. Interactions with Other Substances Affecting Toxicity

Consideration of the toxicity of molybdenum cannot be separated from consideration of the complicated interactions of molybdenum, copper, and sulfur. The interactions are not only complicated, but they differ strikingly in ruminants and rats. In summary, the antagonism of copper metabolism by molybdenum (as molybdate ion) in ruminants occurs at low concentrations of molybdenum (less than 10 ppm), is exacerbated by dietary sulfur, and results in tissue copper depletion, whereas in rats it occurs at high concentrations of molybdenum (greater than 100 ppm), is alleviated by dietary sulfur (with adequate copper), and results in copper accretion in the tissues (Cunningham and Hogan, 1959; Dick, 1956; Evans and Davis, 1976; Gray and Daniel, 1964; Marcilese et al., 1969; Suttle, 1973, 1980, 1983). The molybdenum-copper-sulfur interaction can also be modified by other dietary factors: Dick (1956) showed that high dietary manganese could block the limiting effect of molybdenum on copper retention in sheep, even in the presence of sulfate, and that with a high-protein diet, the combination of molybdenum and manganese could severely limit copper retention. A high-protein diet was found to partially reverse molybdenum toxicity in the rat (Bandyopadhyay et al., 1981). Molybdenum toxicity can be completely reversed by increasing the ratio of copper to molybdenum in ruminants, but not in nonruminants (Underwood, 1976).

VII. TREATMENT

There is no specific treatment for molybdenum toxicity in humans. Victims of acute poisoning should be given supportive care and removed from the source of exposure. Symptoms of molybdenum toxicity in many animal species can be reversed by supplementation with copper.

VIII. TYPICAL EXPOSURE LIMITS/BODY BURDEN/TOXIC LIMITS

A variety of estimates for the daily dietary intake of molybdenum has been reported. The molybdenum content of a two-day hospital diet was determined to be 369 ug/day (Schroeder et al., 1970). The mean daily intakes of five subjects in the United States on a long-term balance trial ranged from 99 to 460 ug/day (Schroeder et al., 1970). Based on analysis of foods collected in a grocery basket sampling program together with food consumption data, Tsongas et al. (1980) estimated daily dietary intakes of molybdenum in the United States to vary between 120 and 240 ug/day depending on age, sex, and income. In the United Kingdom, total dietary intake based on analysis of diet homogenates was estimated to be 128 ± 34 ug by Hamilton and Minski (1972/73) and to range from 89 to 109 ug depending on the method of calculation by Evans et al. (1985). In India, intakes of 540 ug/day have been produced by consumption of sorghum containing a high concentration of molybdenum (Deosthale and Gopalan, 1974). In a molybdenum-rich province of the Soviet Union, intakes have been estimated to range from 10,000 to 15,000 ug/day (Kovalsky et al., 1961). Mertz (1976) noted that the reported ranges differ by a factor of 150, which is greater than the known safety factors between marginally deficient and marginally excessive levels for several anionic trace elements.

Molybdenum intake from drinking water can vary considerably. In 1962, Durfor and Becker (1964) [cited by Carson et al. (1986)] found a median molybdenum level of 1.4 ug/L in the finished waters of 100 large U.S. cities, with values ranging from not detectable to 68 ug/L. Kopp (1969) [cited by Carson et al. (1986)] detected an even wider range of values in 380 finished waters, with 30% having detectable molybdenum levels ranging from 3 to 1024 ug/L and a median of 86 ug/L. Molybdenum is not significantly removed by usual water treatment processes (Safe Drinking Water Committee, 1977).

A Recommended Dietary Allowance has not been established for molybdenum, but intakes ranging from 150 to 500 ug/day have been proposed as "safe and adequate" levels to meet the nutritional requirements of adults (Committee on Dietary Allowances, Food and Nutrition Board, 1980). Evidence on the biological and behavioral aspects of aging has not suggested a higher requirement for the elderly (Solomons, 1986).

Snyder et al. (1975) estimated the total body burden of molybdenum in a 70-kg reference man to be 9.5 mg with 4.5 mg in the soft tissue. Their calculations for daily balance in reference man include an intake of 300 ug from food and fluids and less than 0.1 ug from airborne sources and losses of 150 ug in urine, 120 ug in feces, 20 ug in sweat, and trace amounts in hair and other fluids.

Carson et al. (1986) cite the following inhalation exposure limits given by the American Council of Government Industrial Hygienists in 1983: the threshold limit value as a time-weighted average for an 8-hour day is 10 mg/m^3 for insoluble molybdenum and 5 mg/m^3 for soluble molybdenum compounds. The Occupational Safety and Health Administration has set a permissible exposure limit of 15 mg/m^3 for insoluble molybdenum compounds and 5 mg/m^3 for soluble compounds [cited by Carson et al. (1986)].

Sittig (1985) notes that the Soviet Union has set a molybdenum limit in open water of 0.5 mg/L, but that the World Health Organization has not set a limit. The Environmental Protection Agency has suggested a permissible ambient goal of 70 ug/L (Sittig, 1985).

IX. INDICATORS OF EXCESSIVE ACCUMULATION

A. Index

Mertz (1976) notes that humans are not well protected against deficient or excessive exposures to molybdenum in the environment and that differential exposures are readily reflected in tissue contents of the element. Thus, the measurement of molybdenum levels in a readily accessible tissue such as blood may provide an indication of exposure. The essential function of molybdenum in the enzyme xanthine oxidase also offers the possibility of measuring a biological response to excessive exposure to molybdenum. Saturation of this enzyme has not been demonstrated, and its activity increases over a large range of intakes (Mertz, 1977).

B. Analytical Methodology

Colorimetric methods employing dithiol provide a simple, rapid, precise, and sensitive procedure for determining molybdenum in biologic and other samples (Quin and Brooks, 1975; Cardenas and Mortenson, 1974). Biologic samples are ashed at 550°C and leached with HCl; then the dithiol-molybdenum complex is extracted with isoamyl acetate. Interference from metals such as iron and tungsten and from other constituents in biological material has been found to be negligible. Other colorimetric assays with reagents such as thiocyanate (Dick and Bingley, 1951) and N-o-tolyl-o-methoxy-benzohydroxamic acid (Abbasi, 1981) also have been found to provide fairly selective and sensitive measurements of molybdenum.

Berman (1980) noted the slow development of instrumental methods for the analysis of molybdenum, but reported some applications of spectrographic analyses, neutron activation analysis, X-ray fluorescence, flame atomic absorption spectrometry, and graphite furnace analysis to the determination of molybdenum in biological materials. Greater attention needs to be devoted to developing standardized determinations of molybdenum, with certified biological reference materials (Mertz, 1976).

C. Basis for Interpretative Criteria

Standards for the interpretation of blood levels of molybdenum have not been established. Allaway et al. (1968) determined the molybdenum content of blood collected from adult males at 19 sites in 15 different states in the United States. Of 229 samples, 48 had detectable levels of molybdenum (> 0.5 ug/100 ml). These samples were from nine geographic sites, with mean values ranging from 0.50 to 15.73 ug/100 ml. When two sites with unusually high values were eliminated, values ranged from 0.50 to 3.37 ug/100 ml.

Bala and Lifshits (1966) found the mean concentration of molybdenum in whole blood of healthy subjects to be 1.47 ug/100 ml, with slightly greater amounts associated with the red cells than with plasma proteins. The same investigators also observed an increase in molybdenum concentration in the red cells of patients with leukemia, and decreases in the amount of molybdenum in both red cells and plasma in patients with various types of anemia.

In their review, Friberg and Lener (1986) concluded that although the molybdenum level of whole blood varies substantially among individuals, most data support a normal level of a few ug/L.

Subjects in a high-molybdenum area of the Soviet Union were shown to have higher levels of both molybdenum and xanthine oxidase activity in blood than controls in a normal-molybdenum region (Kovalsky et al., 1961). Subjects in the high-molybdenum area who were affected by a gout-like disease had even higher levels than others in the same region who were not affected (Table C.4).

Walravens et al. (1979) measured plasma molybdenum in workers exposed to molybdenum dust and control subjects. In 14 of of the 24 control subjects, plasma levels were below the limit of detection (0.5 ug/100 ml); in the remaining 10 controls, plasma molybdenum levels ranged from 0.5 to 3.4 ug/100 ml. In the 25 exposed workers, plasma molybdenum levels were 0.9 to 36.5 ug/100 ml. Delves (1985) reported that normal serum molybdenum levels were much lower than those seen in the controls of this study, between 2 and 12 nmol/l (19-115 ng/100 ml).

D. Quality Control/Quality Assurance

Some investigators caution against the use of stainless steel needles or containers for drawing blood or storing samples intended for molybdenum analysis because of the possibility of leaching exogenous molybdenum into the sample.

Table C.4. Blood molybdenum, xanthine oxidase activity, and uric acid, and uric acid excretion in human subjects*

Area	Blood Molybdenum	Xanthine Oxidase Activity**	Blood Uric Acid	Urine Uric Acid
	(ng/g)	(units)	(mg/100 ml)	(mg/24 hr)
High molybdenum				
Sick	310	2.1	8.1	824
Healthy	170	1.27	5.3	649
Average	220	1.52	6.2	707
Normal molybdenum	60	1.0	3.8	432

* Data from Kovalsky et al. (1961); table adapted from Mertz (1976).

** Arbitrary units.

REFERENCES

Abbasi, S.A. 1981. Toxicity of molybdenum and its trace analysis in animal tissues and plants. Int. J. Environ. Anal. Chem. 10:305-308.

Abumrad, N.N.; Schneider, A.J.; Steel, D.; Rogers, L.S. 1981. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. Am. J. Clin. Nutr. 34:25512559.

Alexander, F.W.; Clayton, B.E.; Delves, H.T. 1974. Mineral and trace-metal balances in children receiving normal and synthetic diets. Q. J. Med. 43:89-111.

Allaway, W.H. 1977. Perspectives on molybdenum in soils and plants. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 2. The geochemistry, cycling, and industrial uses of molybdenum. New York: Marcel Dekker, Inc. p.317-339.

Allaway, W.H.; Kubota, J.; Losee, F.; Roth, M. 1968. Selenium, molybdenum, and vanadium in human blood. Arch. Environ. Health 16:342-348.

Anonymous. 1975. Genu valgum due to fluoride toxicity. Nutr. Rev. 33:76-77.

Anonymous. 1987. Molybdenum deficiency in TPN. Nutr. Rev. 45:337-341.

Arrington, L.R.; Davis, G.K. 1953. Molybdenum toxicity in the rabbit. J. Nutr. 51:295-304.

Arthur, D.; Motzok, I.; Branton, H.D. 1958. Interaction of dietary copper and molybdenum in rations fed to poultry. Poultry Sci. 37:1181 (Abstract).

Bala, Y.M.; Lifshits, V.M. 1966. Content of trace elements in the blood in leukemia and anemia. Report II: molybdenum and chromium. Fed. Proc. Transl. Suppl. 25:370-372.

Bandyopadhyay, S.K.; Chatterjee, K.; Tiwari, R.K.; Mitra, A.; Banerjee, A.; Ghosh, K.K.; Chatterjee, G.C. 1981. Biochemical studies on molybdenum toxicity in rats: effects of high protein feeding. Int. J. Vit. Nutr. Res. 51:401-409.

Barrow, N.J. 1977. Factors affecting the molybdenum status of soils. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 2. The geochemistry, cycling, and industrial uses of molybdenum. New York: Marcel Dekker, Inc. p.583-595.

Bell, M.C.; Diggs, B.G.; Lowrey, R.S.; Wright, P.L. 1964. Mo^{99} metabolism in swine and cattle as affected by stable molybdenum. Fed. Proc. Fed. Am. Soc. Exp. Biol. 23:873 (Abstract).

Berman, E. 1980. Toxic metals and their analysis. London: Heyden & Son Ltd. p.161-169.

Bibr, B.; Lener, J. 1973. Excretion of molybdenum by experimental animals. Physiol. Bohemoslov. 22:167-178.

Bibr, B.; Lener, J. 1974. Retention of a single dose of molybdenum in the tissues of experimental animals. Physiol. Bohemoslov. 23:341-342 (Abstract).

Briese, F.W. 1976. Geographic variation of mortality and cancer morbidity in Colorado. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.287-315.

Buck, W.B.; Ewan, R.C. 1973. Toxicology and adverse effects of mineral imbalance. Clin. Toxicol. 6:459-485.

Cardenas, J.; Mortenson, E. 1974. Determination of molybdenum and tungsten in biological materials. Anal. Biochem. 60:372-381.

Carson, B.L.; Ellis, H.V., III; McCann, J.L. 1986. Toxicology and biological monitoring of metals in humans including feasibility and need. Chelsea, MI: Lewis Publishers, Inc. p.157-161.

Chan, W-Y.; Rennert, O.M. 1985. Genetic trace metal disturbances. J. Am. Coll. Nutr. 4:39-48.

Cohen, H.J.; Drew, R.T.; Johnson, J.L.; Rajagopalan, K.V. 1973. Molecular basis of the biological function of molybdenum: the relationship between sulfite oxidase and the acute toxicity of bisulfite and SO2. Proc. Nat. Acad. Sci. 70:3655-3659.

Colmano, G. 1973. Molybdenum toxicity: abnormal cellular division of teratogenic appearance in Euglena gracilis. Bull. Environ. Contam. Toxicol. 9:361-364.

Committee on Dietary Allowances, Food and Nutrition Board. 1980. Recommended dietary allowances. 9th edition. Washington, DC: National Academy of Sciences. p.164-165.

Cunningham, I.J.; Hogan, K.G. 1958. The influence of diet on the copper and molybdenum contents of hair, hoof and wool. N.Z. J. Agric. Res. 1:841-846.

Cunningham, I.J.; Hogan, K.G. 1959. High molybdenum intake and the thrift of young sheep. N.Z. J. Agric. Res. 2:134-144.

Cunningham, I.J.; Hogan, K.G.; Lawson, B.M. 1959. The effect of sulphate and molybdenum on copper metabolism in cattle. N.Z. J. Agric. Res. 2:145-152.

Curzon, M.E.J.; Kubota, J.; Bibby, B.G. 1971. Environmental effects of molybdenum on caries. J. Dent. Res. 50:74-77.

Dale, S.E.; Ewan, R.C.; Speer, V.C.; Zimmerman, D.R. 1973. Copper, molybdenum and sulfate interaction in young swine. J. Anim. Sci. 37:913-917.

Davies, R.E.; Reid, B.L.; Kurnick, A.A.; Couch, J.R. 1960. The effect of sulfate on molybdenum toxicity in the chick. J. Nutr. 70:193-198.

Delves, H.T. 1985. Assessment of trace element status. Clin. Endocrinol. Metab. 14:725-760.

Deosthale, Y.G.; Gopalan, C. 1974. The effect of molybdenum levels in sorghum (Sorhum vulgare Pers.) on uric acid and copper excretion in man. Br. J. Nutr. 31:351-355.

De Renzo, E.C.; Kaleita, E.; Heytler, P.G.; Oleson, J.J.; Hutchings, B.L.; Williams, J.H. 1953. Identification of the xanthine oxidase factor as molybdenum. Arch. Biochem. Biophys. 45:247-253.

Dick, A.T. 1953. The effect of inorganic sulphate on the excretion of molybdenum in the sheep. Austr. Vet. J. 29:18-26.

Dick, A.T. 1954. Preliminary observations on the effect of high intakes of molybdenum and of inorganic sulphate on blood copper and on fleece character in crossbred sheep. Austr. Vet. J. 30:196-202.

Dick, A.T. 1956. Molybdenum in animal nutrition. Soil Sci. 81:229-236.

Dick, A.T.; Bingley, J.B. 1951. Further observations on the determination of molybdenum in plant and animal tissue. Austr. J. Exp. Biol. Med. Sci. 29:459-462.

Durfor, C.N.; Becker, E. 1964. Public water supplies of the 100 largest cities in the United States, 1962. U.S. Geological Survey Water-Supply Paper 1812. Washington, DC: U.S. Government Printing Office.

Engel, R.W.; Price, N.O.; Miller, R.F. 1967. Copper, manganese, cobalt, and molybdenum balance in pre-adolescent girls. J. Nutr. 92:197-204.

Eolian, S.L. 1965. [On the effect of molybdenum (molybdate) on the nervous system.] Zh. Eskp. Klin. Med. 5:70-72. (In Russian).

Evans, J.L.; Davis, G.K. 1976. Copper-sulfur-molybdenum interrelationship(s) in the growing rat evaluated via the factorial arrangement of diet treatments. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.149-161.

Evans, W.H.; Read, J.I.; Caughlin, D. 1985. Quantification of results for estimating elemental dietary intakes of lithium, rubidium, strontium, molybdenum, vanadium and silver. Analyst 110:873-877.

Fairhall, L.T.; Dunn, R.C.; Sharpless, N.E.; Pritchard, E.A. 1945. The toxicity of molybdenum. Public Health Bulletin No. 293. U.S. Public Health Service. 36p.

Ferguson, W.S.; Lewis, A.H.; Watson, S.J. 1938. Action of molybdenum in nutrition of milking cattle. Nature 141:553.

Ferguson, W.S.; Lewis, A.H.; Watson, S.J. 1943. The teart pastures of Somerset: I. The cause and cure of teartness. J. Agric. Sci. 33:44-51.

Friberg, L. 1979. Molybdenum. In: Friberg, L.; Nordberg, G.F.; Vouk, V.B., eds. Handbook on the toxicology of metals. New York: Elsevier/North-Holland Biomedical Press. p.531-539.

Friberg, L.; Lener, J. 1986. Molybdenum. In: Friberg, L.; Nordberg, G.F.; Vouk, V., eds. Handbook on the toxicology of metals, 2nd edition. Elsevier Science Publishers. p.446-461.

Goyer, R.A. 1986. Toxic effects of metals. In: Klaassen, C.D.; Amdur, M.O.; Doull, J., eds. Casarett and Doull's toxicology: the basic science of poisons. 3rd edition. New York: Macmillan Publishing Company. p.582-635.

Gray, L.F.; Daniel, L.J. 1954. Some effects of excess molybdenum on the nutrition of the rat. J. Nutr. 84:31-37.

Gray, L.F.; Daniel, L.J. 1964. Effect of the copper status of the rat on the copper-molybdenum-sulfate interaction. J. Nutr. 84:31-37.

Gray, L.F.; Ellis, G.H. 1950. Some interrelationships of copper, molybdenum, zinc and lead in the nutrition of the rat. J. Nutr. 40:441-452.

Gunnison, A.F.; Sellakumar, A.; Currie, D.; Snyder, E.A. 1987. Distribution, metabolism and toxicity of inhaled sulfur dioxide and endogenously generated sulfite in the respiratory tract of normal and sulfite oxidase-deficient rats. J. Toxicol. Environ. Health 21:141-162.

Hadjimarkos, D.M. 1973. Trace elements and dental health. In: Hemphill, D.D., ed. Trace substances in environmental health - VII. Proceedings of University of Missouri's 7th Annual Conference on Trace Substances in Environmental Health. Columbia, MO: University of Missouri. p.35-40.

Hamilton, E.I.; Minski, M.J. 1972/1973. Abundance of the chemical elements in man's diet and possible relations with environmental factors. Sci. Total Environ. 1:375-394.

Hansen, S.R.; Morehardt, J.E. 1987. Identification of potential substances-of-concern in agricultural drainage waters from the San Joaquin Valley: a screening level analysis. Prepared for the San Joaquin Valley Drainage Program, Sacramento, CA under EA Prop BAC 72A by E.A. Engineering, Science, and Technology, Inc., Lafayette, CA.

Hazell, T. 1985. Minerals in foods: dietary sources, chemical forms, interactions, bioavailability. World Rev. Nutr. Diet. 46:1-123.

Higgins, E.S.; Richert, D.A.; Westerfeld, W.W. 1956. Molybdenum deficiency and tungstate inhibition studies. J. Nutr. 59:539-559.

Hornick, S.B.; Baker, D.E.; Guss, S.B. 1977. Crop production and animal health problems associated with high soil molybdenum. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 2. The geochemistry, cycling, and industrial uses of molybdenum. New York: Marcel Dekker, Inc. p.665-684.

Huisingh, J.; Matrone, G. 1976. Interactions of molybdenum in animal nutrition. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.125-148.

Jarrell, W.M.; Page, A.L.; Elseewi, A.A. 1980. Molybdenum in the environment. Residue Rev. 74:1-43.

Jeter, M.A.; Davis, G.K. 1954. The effect of dietary molybdenum upon growth, hemoglobin, reproduction and lactation of rats. J. Nutr. 54:215-220.

Johnson, J.L.; Rajagopalan, K.V. 1976. Experimental molybdenum deficiency in the rat. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.201-219.

Johnson, J.L.; Rajagopalan, K.V.; Cohen, H.J. 1974. Molecular basis of the biological function of molybdenum: effect of tungsten on xanthine oxidase and sulfite oxidase in the rat. J. Biol. Chem. 249:859-866.

Katyal, J.C.; Randhawa, N.S. 1983. Micronutrients. FAO Fertilizer and Plant Nutrition Bulletin 7. Rome: Food and Agriculture Organization of the United Nations. p.69-76.

Kopp, J.F. 1969. The occurrence of trace elements in water. In: Hemphill, D.D., ed. Trace substances in environmental health - III. Proceedings of the University of Missouri's Third Annual Conference on Trace Substances in Environment Health, 1969. Columbia: University of Missouri. p.59-73.

Kosarek, L.J.; Winston, P.W. 1975. A model depicting rat tissue molybdenum concentration through four generations. Am. Zool. 15:818 (Abstract).

Kosarek, L.J.; Winston, P.W. 1977. Absorption of molybdenum-99 (Mo-99) as molybdate with various doses in the rat. Fed. Proc. Fed. Am. Soc. Exp. Biol. 36:1106 (Abstract).

Kovalsky, V.V.; Yarovaya, G.A.; Shmavonyan, D.M. 1961. [The change in purine metabolism of humans and animals under the conditions of molybdenum biogeochemical provinces.] Zh. Obshch. Biol. 22:179-191. (In Russian).

Kratzer, F.H. 1952. Effect of dietary molybdenum upon chicks and poults. Proc. Soc. Exp. Biol. Med. 80:483-486.

Kselikova, M.; Bibr, B.; Lener, J. 1974. Radioisotope (^{99}Mo) study of the kinetics of molybdenum clearance from the blood and of the role of blood components. Physiol. Bohemoslov. 23:83-88.

Kselikova, M.; Bibr, B.; Lener, J. 1977. Interaction of alpha T2-macroglobulin with molybdenum in human and rat serum. Physiol. Bohemslov. 26:573-575.

Kubota, J. 1977. Molybdenum status of United States soils and plants. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 2. The geochemistry, cycling, and industrial uses of molybdenum. New York: Marcel Dekker, Inc. p.555-581.

Lener, J.; Bibr, B. 1979. Biliary excretion and tissue distribution of penta- and hexavalent molybdenum in rats. Toxicol. Appl. Pharmacol. 51:259-263.

Lener, J.; Bibr, B. 1984. Effect of molybdenum on the organism (a review). J. Hyg. Epidemiol. Microbiol. Immunol. 28:405-419.

Lener, J.; Bibr, B.; Kselikova, M.; Marik, T. 1979. Peripheral membrane proteins labelling of erythrocytes with ^{99}Mo. Eur. J. Nucl. Med. 4:119 (Abstract).

Lener, J.; Deyl, Z.; Bibr, B.; Adam, M. 1976. Accumulation of molybdenum in the skin and tendons of Wistar rats. Physiol. Bohemoslov. 25:453-454 (Abstract).

Luo, X.M.; Wei, H.J.; Yang, S.P. 1983. Inhibitory effects of molybdenum on esophageal and forestomach carcinogenesis in rats. J. Nat. Cancer Inst. 71:75-80.

Mahler, H.R.; Green, D.E. 1954. Metallo-flavoproteins and electron transport. Science 120:7-12.

Maltoni, C. 1974. Occupational carcinogenesis. In: Maltoni, C., ed. Advances in tumour prevention, detection and characterization. Vol. 2. Cancer detection and prevention. Amsterdam: Excerpta Medica. p.19-26.

Marcilese, N.A.; Ammerman, C.B.; Valsecchi, R.M.; Dunavant, B.G.; Davis, G.K. 1969. Effect of dietary molybdenum and sulfate upon copper metabolism in sheep. J. Nutr. 99:177-183.

Mason, J. 1986. Thiomolybdates: mediators of molybdenum toxicity and enzyme inhibitors. Toxicology 42:99-109.

McCarter, A.; Riddell, P.E.; Robinson, G.A. 1962. Molybdenosis induced in laboratory rabbits. Can. J. Biochem. Physiol. 40:1415-1425.

Mertz, W. 1976. Defining trace element deficiencies and toxicities in man. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.267-285.

Mertz, W. 1977. Criteria for adequacy and safety of trace elements in animal nutrition. J. Anim. Sci. 44:469-474.

Mills, C.F.; Monty, K.J.; Ichihara, A.; Pearson, P.B. 1958. Metabolic effects of molybdenum toxicity in the rat. J. Nutr. 65:129-142.

Misra, S.G.; Mishra, K.C.; Mishra, P.C. 1977. Retention and release of molybdenum by soils. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 2. The geochemistry, cycling, and industrial uses of molybdenum. New York: Marcel Dekker, Inc. p.597-618.

Neilands, J.B.; Strong, F.M.; Elvehjem, C.A. 1948. Molybdenum in the nutrition of the rat. J. Biol. Chem. 172:431-439.

Ostrom, C.A.; Van Reen, R.; Miller, C.W. 1961. Changes in the connective tissue of rats fed toxic diets containing molybdenum salts. J. Dent. Res. 40:520-528.

Parker, G.A. 1986. Molybdenum. In: Hutzinger, O., ed. The handbook of environmental chemistry. Vol. 3, Part D. Anthropogenic compounds. New York: Springer-Verlag. p.217-240.

Pitt, M.A. 1976. Molybdenum toxicity: interactions between copper, molybdenum and sulphate. Agents Actions 6:758-769.

Quin, B.F.; Brooks, R.R. 1975. The rapid colorimetric determination of molybdenum with dithiol in biological, geochemical and steel samples. Anal. Chim. Acta 74:75-84.

Rajagopalan, K.V. 1984. Molybdenum. In: Frieden, E., ed. Biochemistry of the essential ultratrace elements. New York: Plenum Press. p.149-174.

Rajagopalan, K.V. 1987. Molybdenum -- an essential trace element. Nutr. Rev. 45:321-328.

Richert, D.A.; Westerfeld, W.W. 1953. Isolation and identification of the xanthine oxidase factor as molybdenum. J. Biol. Chem. 203:915-923.

Robinson, G.A.; Valli, V.E.O.; McSherry, B.J.; McCarter Pepino, A. 1969. The survival of DF^{32}P-labelled erythrocytes in molybdate-fed rabbits. Can. J. Physiol. Pharmacol. 47:343-347.

Robinson, M.F.; McKenzie, J.M.; Thomson, C.D.; van Rij, A.L. 1973. Metabolic balance of zinc, copper, cadmium, iron, molybdenum and selenium in young New Zealand women. Br. J. Nutr. 30:195-205.

Rosoff, B.; Spencer, H. 1964. Fate of molybdenum-99 in man. Nature 202:410-411.

Rosoff, B.; Spencer, H. 1973. The distribution and excretion of molybdenum-99 in mice. Health Phys. 25:173-175.

Rossman, T.G.; Molina, M. 1986. The genetic toxicology of metal compounds: II. Enhancement of ultraviolet light-induced mutagenesis in Escherichia coli WP2. Environ. Mutagen. 8:263-271.

Rossman, T.G.; Molina, M.; Meyer, L.W. 1984. The genetic toxicology of metals: I. Induction of prophage in E. coli WP2 ( ). Environ. Metagen. 6:59-69.

Rudman, D.; Williams, P.J. 1985. Nutrient deficiencies during total parenteral nutrition. Nutr. Rev. 43:1-13.

Safe Drinking Water Committee, National Research Council. 1977. Drinking water and health. Washington, DC: National Academy of Sciences.

Schrauzer, G.N. 1976. Molybdenum in biological nitrogen fixation. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.243-265.

Schroeder, H.A. 1971. Metals in the air. Environment 13:18-32.

Schroeder, H.A.; Balassa, J.J.; Tipton, I.H. 1970. Essential trace metals in man: molybdenum. J. Chron. Dis. 23:481-499.

Shimkin, M.B.; Stoner, G.D..; Theiss, J.C. 1977. Lung tumor response in mice to metals and metal salts. Adv. Exp. Med. Biol. 91:85-91.

Sittig, M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd edition. Park Ridge, NJ: Noyes Publications. p.137-139.

Snyder, W.S.; Cook, M.J.; Nasset, E.S.; Karhausen, L.R.; Parry Howells, G.; Tipton, I.H. 1975. Report of the Task Group on Reference Man. International Commission on Radiological Protection. No. 23. New York: Pergamon Press.

Solomons, C.C.; Ernisse, D.J.; Handrich, E.M. 1973. Skeletal biology of molybdenum. In: Hemphill, D.D., ed. Trace substances in environmental health - VII. Proceedings of University of Missouri's 7th Annual Conference on Trace Substances in Environmental Health. Columbia, MO: University of Missouri. p.233-239.

Solomons, N.W. 1986. Trace elements in nutrition of the elderly. 2. SADDIs for copper, manganese, selenium, chromium, molybdenum, and fluoride. Postgrad. Med. 79:251-263.

Spence, J.A.; Suttle, N.F.; Wenham, G.; El-Gallad, T.; Bremner, I. 1980. A sequential study of the skeletal abnormalities which develop in rats given a small dietary supplement of ammonium tetrathiomolybdate. J. Comp. Pathol. 90:139-153.

State Water Resources Control Board. 1987. Regulation of Agricultural Drainage to the San Joaquin River. Order No. WQ 85-1. Technical Committee Staff of the State Water Resources Control board and Central Valley Regulatory Water Control Board. Available from: State Water Resources Control Board.

Stokinger, H.E. 1981. The metals. In: Clayton, G.D.; Clayton, F.E., eds. Patty's industrial hygiene and toxicology, 3rd edition, Vol. 2A. New York: John Wiley & Sons. p.1807-1820.

Suttle, N.F. 1973. The nutritional significance of the Cu:Mo interrelationship to ruminants and non-ruminants. In: Hemphill, D.D., ed. Trace substances in environmental health - VII. Proceedings of University of Missouri's 7th Annual Conference on Trace Substances in Environmental Health. Columbia, MO: University of Missouri. p.245-248.

Suttle, N.F. 1980. The role of thiomolybdates in the nutritional interactions of copper, molybdenum, and sulfur: fact or fantasy? Ann. NY Acad. Sci. 355:195-207.

Suttle, N.F. 1983. A role for thiomolybdates in the Cu x Mo x S interaction in ruminant nutrition. In: Bratter, P.; Schramel, P., eds. Trace element analytical chemistry in medicine and biology. Vol. 2. New York: Walter de Gruyter. p.599-609.

Tipton, I.H.; Cook, M.J. 1963. Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys. 9:103-145.

Tipton, I.H.; Stewart, P.L.; Dickson, J. 1969. Patterns of elemental excretion in long term balance studies. Health Phys. 16:455-462.

Tsongas, T.A.; Meglen, R.R.; Walravens, P.A.; Chappell, W.R. 1980. Molybdenum in the diet: an estimate of average daily intake in the United States. Am. J. Clin. Nutr. 33:1103-1107.

Underwood, E.J. 1976. Molybdenum in animal nutrition. In: Chappell, W.R.; Peterson, K.K., eds. Molybdenum in the environment. Vol.1. The biology of molybdenum. New York: Marcell Dekker, Inc. p.9-31.

Underwood, E.J. 1977. Trace elements in human and animal nutrition. 4th edition. New York: Academic Press. p.109-131.

Van Campen, D.R.; Mitchell, E.A. 1965. Absorption of Cu^{64}, Zn^{65}, Mo^{99}, and Fe^{59} from ligated segments of rat gastrointestinal tract. J. Nutr. 86:120-124.

Van Reen, R. 1959. The specificity of the molybdate-sulfate interrelationship in rats. J. Nutr. 68:243-250.

Venitt, S.; Levy, L.S. 1974. Mutagenicity of chromates in bacteria and its relevance to chromate carcinogenesis. Nature 250:493-495.

Venugopal, B.; Luckey, T.D. 1978. Metal toxicity in mammals. 2. Chemical toxicity of metals and metalloids. New York: Plenum Press. p.253-257.

Walravens, P.A.; Moure-Eraso, R.; Solomons, C.C.; Chappell, W.R.; Bentley, G. 1979. Biochemical abnormalities in workers exposed to molybdenum dust. Arch. Environ. Health 34:302-308.
Ward, G.M. 1978. Molybdenum toxicity and hypocuprosis in ruminants: a review. J. Anim. Sci. 46:1078-1085.

Weast, R.C., editor. 1983-1984. CRC handbook of chemistry and physics. 64th edition. Boca Raton, FL: CRC Press. p.B-22, B-23.

Wei, H-J.; Luo, X-M.; Yang, S.P. 1985. Effects of molybdenum and tungsten on mammary carcinogenesis in SD rats. J. Nat. Cancer Inst. 74:469-473.

Westerfeld, W.W.; Richert, D.A. 1953. Distribution of the xanthine oxidase factor (molybdenum) in foods. J. Nutr. 51:85-95.

Widjajakusuma, M.C.R.; Basrur, P.K.; Robinson, G.A. 1973. Thyroid function in molybdenotic rabbits. J. Endocrinol. 57:419-424.

Williams, M.A.; Van Reen, R. 1956. Molybdenum toxicity in the rat. Proc. Soc. Exp. Biol. Med. 91:638-641.

Windholz, M., editor. 1976. The Merck index, 9th edition. Rahway, NJ: Merck & Co. p.6061-6062.

Winston, P.W.; Franzen, D.K.; Wimberg, S.L.; Reid, E.H. 1985. Comparison of absorption patterns of dietary molybdenum in different forms. In: Mills. C.F.; Bremner, I.; Chesters, J.K., eds. Trace elements in man and animals - TEMA 5. Aberdeen: Commonwealth Agricultural Bureaux. p.531-533.

Winston, P.W.; Heppe, M.S.; Hoffman, L.; Kosarek, L.J.; Spangler, R.S. 1976. Physiological adaptations to excess molybdenum ingested over several generations. In: Chappell, W.R., Peterson, K.K., eds. Molybdenum in the environment. Vol. 1. The biology of molybdenum. New York: Marcel Dekker, Inc. p.185-200.

Winston, P.W.; Hoffman, L.; Smith, W. 1973. Increased weight loss in molybdenum-treated rats in the cold. In: Hemphill, D.D., ed. Trace substances in environmental health - VII. Proceedings of University of Missouri's 7th Annual Conference on Trace Substances in Environmental Health. Columbia, MO: University of Missouri. p.241-244.

Winston, P.W.; Trainor, W.P. 1978. Effect of molybdenum in slight excess on plasma glucose and weight loss after heat stress in rats. In: Hemphill, D.D., (ed). Trace substances in environmental health. Vol. XII. Columbia, MO: University of Missouri.

Yang, S.P.; Luo, X.-M.; Wei, H.-J. 1985. Effect of molybdenum and tungsten on carcinogenesis. In: Mills, C.F.; Bremner, I.; Chesters, J.K., eds. Trace elements in man and animals - TEMA 5. Aberdeen: Commonwealth Agricultural Bureaux. p.160-161.

P00001922